(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 January 2001 (04.01.2001)

PCT

(10) International Publication Number
WO 01/00273 A1

(51) International Patent Classification[7]: A61N 1/05

(21) International Application Number: PCT/US00/17222

(22) International Filing Date: 23 June 2000 (23.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/141,202 25 June 1999 (25.06.1999) US

(71) Applicant *(for all designated States except US)*: **EMORY UNIVERSITY** [US/US]; 1380 S. Oxford Road, Atlanta, GA 30322 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **PUSKAS, John, D.** [CA/US]; 854 Carlton Ridge, Atlanta, GA 30322 (US).

(74) Agents: **WARREN, William, L.** et al.; Kilpatrick Stockton LLP, 2400 Monarch Tower, 3424 Peachtree Road, N.E., Atlanta, GA 30326 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

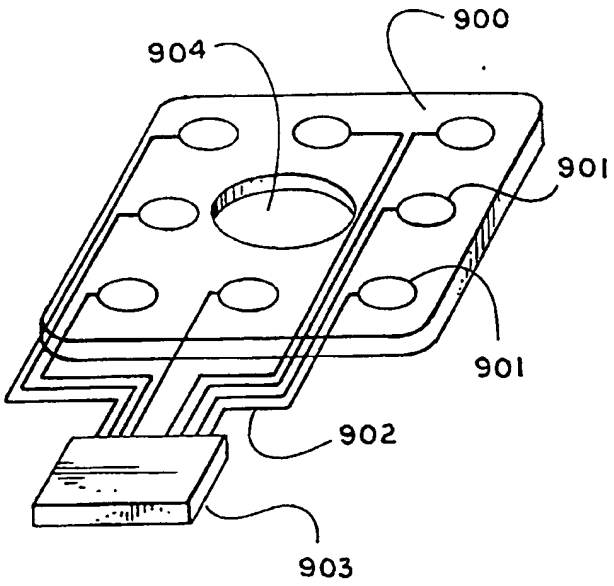
Published:
— *with international search report*

(48) Date of publication of this corrected version:
25 April 2002

(15) Information about Correction:
see PCT Gazette No. 17/2002 of 25 April 2002, Section II

[Continued on next page]

(54) Title: DEVICES AND METHODS FOR VAGUS NERVE STIMULATION



(57) Abstract: The present invention relates to apparatus and methods for electrically inducing, pharmacologically maintaining cardiac asystole. The present invention also provides cutaneous array electrodes (900) that may be used non-invasive to stimulate the vagus nerve.

WO 01/00273 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

DEVICES AND METHODS FOR VAGUS NERVE STIMULATION

Technical Field

The present invention relates to apparatus and methods for electrically-induced and pharmaceutically prolonged cardiac asystole. The present invention is useful for controlling heart beats and escape from asystole during cardiac surgery. The present invention is particularly useful during coronary by-pass surgery when anastomatic formation is readily disrupted by a beating heart.

Background of the Invention

Cardiopulmonary bypass (CPB) and chemical arrest using cardioplegic solutions have traditionally provided surgeons with optimal operative conditions: hemodynamic control and cardiac quiescence. This optimal field has contributed to technical success in increasingly complex cardiac surgical operations. However, there has been recent interest in performing coronary artery bypass surgery without either cardiopulmonary bypass or cardioplegia. The quality of the distal anastomoses is a primary concern among cardiac surgeons who observe and perform coronary artery bypass graft procedures (CABG) unaided by cardiopulmonary bypass or cardioplegic arrest. Coronary artery bypass graft failure rate reported with off-pump coronary grafting range from 3.8 - 8.9%, while traditional CABG on CPB has a reported anastomotic failure rate of less than 1%. This may reflect a difference in anastomotic precision between off-pump CABG and CPB-aided CABG. Although the benefits of avoiding extra-corporeal circulation and global cardioplegia in beating heart procedures are important, they do not outweigh the performance of optimal coronary anastomoses.

The key difference in the anastomotic results between conventional CABG and off-pump CABG (OPCAB) is related to achieving elective asystole during construction of the distal anastomoses. Cardiac motion can be minimized during OPCAB procedures by inducing pharmacological bradycardia by administering beta adrenergic receptor blockers and mechanical

stabilization by a variety of devices. Although these techniques improve operative conditions they only approximate the advantages of elective asystole that can be achieved with CPB and cardioplegia.

A state of Controlled Intermittent Asystole (CIA) would provide brief intervals of cardiac quiescence to facilitate placement of coronary anastomatic structures while avoiding the necessity of a cardiopulmonary bypass and cardioplegia. CIA would thus provide the surgeon with an important advantage otherwise gained only by full cardioplegic arrest on CPB. The CIA technique improves the precision of coronary anastomoses that would otherwise be performed on a beating heart and may reduce graft failure while increasing ease of operation, as described in application WO9909973, incorporated by reference herein in its entirety.

In particular, CIA can be achieved using unilateral (or bilateral) vagus nerve stimulation coupled with pharmacological potentiation of vagal impulses and pharmacological suppression of electromechanical escape activity. It has previously been demonstrated in WO 9817680, incorporated herein by reference in its entirety, that elective Controlled Intermittent Asystole is possible by vagus nerve stimulation after treatment with an acetylcholinesterase inhibitor, a beta-adrenergic receptor blocker, and a calcium channel blocker or combinations thereof. What is required, however, is an integrated system and apparatus that will provide optimal electrical pulses to the vagus nerve to induce cardiac arrest. The intermittent cardiac quiescent periods will be of sufficient duration to allow precise performance of surgical procedures that are not adversely interrupted by escape beats breaking through asystole. What are also required are electrostimulation devices that will permit the identification of the optimal position of an electrode or series of electrodes relative to a vagus nerve to induce asystole. What is further required are means and methods for applying the electric pulse to the nerve, either directly or indirectly and to administer a pharmaceutical composition to potentiate the influence of vagal stimulation on the heart rate, and prolong the period of asystole, thereby increasing the likelihood that the surgical procedure will proceed uninterrupted.

The present invention introduces apparatus, devices and methods that will allow the CIA technique to be performed with ease and precision.

Summary of the invention

The present invention solves the problems described above by providing a convenient apparatus for the application of an electrical pulse to the vagus nerve so as to arrest the heart beat in preparation for diagnostic or therapeutic medical or surgical procedures such as cardiac surgery. The apparatus directs an electrical pulse of optimized intensity and duration at a selected position along the nerve, and thereby induces cardiac quiescence. Spontaneous escape from asystole is prevented pharmacologically. The present invention, therefore, provides the apparatus and methods for the cardiac surgeon to induce a state of Controlled Intermittent Asystole (CIA), thereby greatly easing bypass surgery, significantly improving surgical quality and patient outcome.

The apparatus of the present invention allows the determination of the optimum location for an electrode to apply an electric stimulus to the vagus nerve. The apparatus correlates the response of the heart to the electrical pulse and modifies the stimulus to achieve suppression of the heart beat and then administers an optimized electric pulse to the vagus nerve. Both for safety and to deliberately terminate asystole once the surgical procedure in the heart is completed, the apparatus includes a cardiac pacer to stimulate the heart to escape asystole when this is desired.

The apparatus includes a multi-channel output means with at least one electrode linked to an electric pulse generator, and which will direct the electric pulse to the vagus nerve with efficiency and with minimal damage to the neural tissue. The electrodes are adjustable as to where they may be placed relative to the vagus nerve and offer various degrees of invasiveness. The electrodes of the present invention offer adaptability to the needs of the surgeon, variations in patient anatomy or physiology and the requirements of the cardiac surgical procedures being employed.

Accordingly, an object of the present invention is to provide an apparatus that will permit the surgeon to apply a selected electric pulse stimulus to the vagus nerve so that asystole will be induced.

It is a further object of the present invention to provide an apparatus that optimizes the electrical stimulus to the vagus nerve.

It is yet a further object of the present invention to provide electrodes for the direct or indirect application of an electrical stimulus to the

vagus nerve that minimizes damage to tissue while allowing the surgeon to determine the optimal location for the electrode.

Yet another object of the present invention is to provide methods for the administering of an electrical stimulus to the vagus nerve and a pharmaceutical composition that will result in Controlled Intermittent Asystole.

An advantage of the present invention is that it offers the surgeon an apparatus that integrates the means to electrically stimulate the vagus nerve with the means to determine whether the heart beat is suppressed and will automatically determine the optimum stimulation to the nerve.

Another advantage of the present invention is the induction of a readily regulated and reliable state of asystole, greatly easing cardiac surgical procedures and comfort to the patient.

These and other features, objects and advantages of the invention and preferred embodiments of the present invention will become apparent from the detailed description that follows.

Brief Description of the Drawings

Figure 1 is a schematic arrangement of the vagus nerve stimulator. All of the components of the stimulator are shown as separate entities although it is envisaged that the interrogator, logic circuitry, the pulse generator, the cardiac monitor and the cardiac pacer could be incorporated and integrated electrically and electronically as a single unit in any combination.

Figure 2A shows a longitudinal section through an embodiment of the catheter wire or basket electrode device. Figure 2B shows a transverse section through the catheter device at the plane A-A' of Figure 2A.

Figure 3 shows embodiments of catheter wire or basket electrode devices. Figure 3A shows a wire electrode. Figure 3B shows a wire electrode with arcuate ribs. Figure 3C shows a wire or basket electrode with circumferentially arranged electrodes disposed on longitudinal non-conductive ribs. Figure 3D shows a helical wire electrode. Figure 3E shows a wire electrode wherein the expansion means is shape memory.

Figure 4 shows embodiments of the inflatable balloon electrode device. Figure 4A shows a balloon electrode with longitudinal electrodes. Figure 4B shows a balloon electrode with circumferentially arranged electrodes. Figure 4C shows a balloon electrode with a helical electrode. Figure 4D shows a balloon

electrode with a longitudinal electrode disposed on a longitudinal raised ridge. Figure 4E shows a transverse section through the embodiment of Figure 4D at the plane B-B'. Figure 4F shows a balloon electrode with longitudinal electrodes not fixed to the surface of the balloon and united by a wire yoke.

Figures 5A and B show longitudinal sections through a catheter umbrella electrode device.

Figures 6A-D show embodiments of the clip electrode device.

Figure 7A shows a wire mesh neural electrode. Figure 7B shows cuff neural electrode conforming to the shape of the nerve. Figure 7C shows a transverse section through the cuff electrode at plane C-C'. Figure 7D shows a cuff neural electrode with two separate electrodes.

Figure 8A shows a pad embodiment of cutaneous electrode array. Figure 8B shows a pad electrode with traversing hole to surround the neck. Figure 8C shows an electrode with traversing hole to surround the neck. Figure 8D shows a cutaneous electrode in a necklace configuration. Figure 8E shows a cutaneous electrode in a turtleneck configuration.

Figure 9A shows a tube balloon electrode device for insertion into the trachea or esophagus. Figure 9B shows a tube umbrella electrode device. Figure 9C shows an alternate electrode device of the present invention.

Detailed Description and Preferred Embodiments

The present invention provides devices and methods for achieving Controlled Intermittent Asystole by means of vagus nerve stimulation. While the purpose of the devices is for achieving Controlled Intermittent Asystole status by means of vagus nerve stimulation, the devices are not limited thereto, and it will be recognized that various embodiments of the invention can be used to facilitate other medical or surgical procedures.

The present invention provides apparatus for the regulated electrostimulation of the vagus nerve to induce a state of asystole. The embodiments of the vagal nerve stimulator apparatus also include electrodes, catheters and electrode catheters suitable for applying a selected electrical pulse to the vagus nerve for the purpose of controlling cardiac rhythm. The apparatus include a pulse generator, a cardiac pacer and a cardiac monitoring means. The apparatus further comprises interrogative electronic circuitry and computer

readable software intended that will allow the apparatus to determine the optimal position of an electrode for the delivery of an effective amount of neural electrostimulation to arrest the beating heart. The apparatus of the present invention also includes a cardiac stimulator and control circulatory and switches to revive the heart.

The present invention also provides methods for the induction of Controlled Intermittent Asystole (CIA) by means of the co-administration of an effective amount of a pharmaceutical composition comprising an acetylcholinesterase inhibitor, a beta-adrenergic blocker and a calcium channel blocker and the electrostimulatory impulse that will arrest cardiac activity.

Definitions

The term "electrode" is used herein to mean any conductor used to establish electrical contact with an area of a human. Said area may be, but is not limited to, the surface of the skin, the interior surface of a blood vessel, the gastroentological tract, the respiratory tract, or any other internal or external surface of the anatomy.

The term "cardiac monitoring means" is used herein to mean any device that will measure the frequency or amplitude of the output of the heart. The output parameters include, but are not limited to, the electrical output of the heart, the pulse strength or its frequency, or systolic or diastolic blood pressure. The "cardiac monitoring means" can be, but is not limited to, an electrocardiograph, a sphyngometer, a pulse detector or any other mechanical, electric or electronic device known to one of skill in the art that will detect cardiac activity and translate said activity measurement to an electrical signal.

The term "cardiac pacer" is used herein to mean any device that will induce the heart to beat in a regular or intermittent manner.

The term "electric pulse" is used herein, but is not limited to, a unipolar or bipolar pulse, wherein the unipolar pulse is between a single electrode implanted in, or situated on, a patient, and an electrode electrically connected to the ground and wherein the bipolar pulse is between at least a pair of electrodes in or on the patient, with no electrode being directly grounded.

The terms "electric pulse generator" and "pulse generator" are used herein to mean any device or devices that will deliver an electric pulse of preselected frequency and amplitude. The device will include electronic circuitry

electrically linked to variable switch means to regulate output voltage, frequency and amplitude of the current supplied.

The term "means of supplying an electric pulse" is used herein to mean, but is not limited to an electrically conductive wire, strip or other means known to one of skill in the art, that is electrically connected at one end to a source of electricity and at the other end to the site of delivery of the electricity, such as, but not limited to, an electrode.

The terms "interrogator", 'interrogative device" or "interrogative circuitry" are used herein to mean any computer or electronic circuitry or device, including computer readable software, that will receive the signal for a cardiac monitoring means and adjust the electric pulse delivered by the pulse generator until the cardiac activity is temporarily, substantially or completely eliminated. The "interrogator" will also include circuitry to sequentially assign an output pulse from the pulse generator to at least one electrode of a plurality of electrodes. The interrogator also includes a logic circuit wherein it may integrate the cardiac monitoring means output, the pulse generator and the selected electrode. The pacer also, but not necessarily is electrically linked to the interrogator. The interrogator may be microprocessor based and include software to compare the signal from a cardiac monitoring means and regulate the output of the pulse generator and the cardiac pacer.

The term "catheter" is used herein to mean any tube device that can be introduced into the body of a patient or animal through an orifice or incision thereof. The device includes, but is not limited to, an intravascular catheter, a tracheal catheter or tube, a nasogastric or esophageal tube or catheter or any other tube device that may be introduced into a human or animal.

The term "manual switch" or "manually operable switch" is used herein to mean any switch device operable by foot, hand, voice, or any other means available to the surgeon during the course of surgery and that will override or supplement on automatic switch means such as but not limited to that provides by the interrogator unit.

Pharmaceutical Compositions

The terms "pharmaceutical Controlled Intermittent Asystole composition" or "CIA composition" are used herein to include, but are not limited to, pharmaceutical compositions capable of prolonging a state of cardiac asystole. The pharmaceutical compositions comprise an acetylcholinesterase

inhibitor selected from, but not limited to, donepezil hydrochloride, tacrine hydrochloride, pyridostigmine bromide, neostigmine methylsulfate, edrophonium chloride, physostigmine salicylate, a β-adrenegic receptor inhibitor selected from, but not limited to, sotalol hydrochloride, timolol maleate, esmotol hydrochloride, carteolol hydrochloride, propranolol hydrochloride, betaxolol hydrochloride, penbutolol sulfate, metoprolol tartrate, acebutolol hydrochloride, atenolol, metoprolol succinate, bisoprolol fumarate, and a calcium channel blocker selected from, but not limited to, nifedipine, verapamil hydrochloride, nicardipine hydrochloride, diltiazem hydrochloride, isradipine, nimodipine, amlodipine besylate, felodipine, nifedipine, nisoldipine, and bepridil hydrochloride. In a preferred embodiment, the composition comprises an acetylcholinesterase inhibitor, a beta-adrenergic receptor inhibitor and a calcium channel blocker. In a more preferred embodiment of the present invention the composition comprises between about 0.1 mg/kg body weight to about 100 mg/kg body weight of pyridostigmine, 0.01 mg/kg body weight to about 100 mg/kg body weight of propanolol hydrochloride and between 0.001 mg/kg body weight and 1.0 mg/kg body weight of verapamil hydrochloride. Most preferably the pharmaceutical composition comprises 500 µg/kg body weight of pyridostigmine, 80 µg/kg body weight of propanolol hydrochloride and 50 µg/kg body weight of verapamil hydrochloride.

The preferred method of administering the CIA composition to achieve CIA is as a slow bolus delivered intravenously over a 1-10 minute period. The CIA composition is given to establish a pharmacological background state in which subsequent vagus nerve electrostimulation causes CIA. The CIA composition may be maintained at effective blood concentrations in a human patient by slow continuous or intermittent infusion. Repeated bolus administration may be necessary in some patients. The effects of the CIA composition may be reversed chemically if necessary by intravenous administration of a drug chosen from, but not limited to, atropine sulfate, isoproterenol hydrochloride, and epinephrine hydrochloride.

Abbreviations

The following abbreviations are used in this description. CIA designates Controlled Intermittent Asystole. CABG designates Coronary Artery Bypass Grafting. CPB designates Cardiopulmonary Bypass. OPCAB designates Off Pump Coronary Artery Bypass Grafting, or coronary grafting without the use

of cardiopulmonary bypass, synonymous with beating heart bypass surgery. MIDCAB designates Minimally Invasive Direct Coronary Artery Bypass Grafting, an off-pump grafting procedure, typically performed through a left thoracotomy. E-CABG designates Endoscopic Coronary Artery Bypass Grafting, i.e. CABG performed using endoscopic instruments inserted through small intercostal incisions, and in the absence of a sternotomy or formal thoracotomy. All embodiments of the invention may be used with pump-assisted or entirely off-pump procedures.

Controlled intermittent asystole can be achieved by potentiation of vagal induced bradycardia by means of a pharmacological combination. The chronotropic effect of vagal nerve stimulation in the absence of pharmacological potentiation includes a very brief initial pause followed by "vagal escape" beats and transient bradycardia. Vagus nerve stimulation alone does not produce controlled asystole. On the other hand, increased acetylcholine activity resulting from acetylcholinesterase inhibition, the prevention of electromechanical escape from asystole by beta-adrenergic receptor and calcium channel blockade, and the application of simultaneous vagal stimulation produces a marked potentiation of vagal-induced asystole, and a means of achieving Controlled Intermittent Asystole (CIA). CIA can, therefore, be reproducibly achieved for prolonged periods, or for multiple shorter sequential intervals selected as appropriate for the construction of coronary anastomoses, or other medical or surgical purposes.

It has unexpectedly been found that stimulation of the right vagus nerve combined with administration of the preferred pharmacological composition results in prolonged asystole. While electrical stimulation of the right vagus nerve is preferred, electrostimulation may also be effectively applied to the left vagus nerve or to both nerves simultaneously or sequentially. The site of nerve stimulation can be, but not necessarily, in the neck.

The preferred indirect method and site of stimulation of the vagus nerve is by means of a percutaneous catheter or electrode probe implanted in the internal jugular vein, trachea, esophagus, or a combination thereof. Other preferred locations for vagus nerve stimulation include, but are not limited to, of the right or left vagus nerve or both. The nerve may be stimulated by unipolar excitation, wherein the ground electrode is located at the skin surface, or by direct or indirect bipolar excitation. An internal jugular vein stimulating electrode device can be introduced through the sternotomy via the right atrium, the right atrial appendage, the inferior vena cava or the superior vena cava. It can be

associated with a flow-through cannula, for the purpose of administrating fluids or drugs. A stimulating electrode may also be placed in direct contact with the vagus nerve by thoracoscopy, thoracotomy or sternotomy and during the course of open-chest thoracic surgery. The present invention contemplates the use of any of the presently described devices with the methods for achieving controlled intermittent asystole, including the use of pharmaceutical compositions for achieving the same.

The present invention contemplates implantable catheters having a plurality of electrodes. An electric pulse can be sent to a single electrode or to at least two electrodes randomly or non-randomly selected, either manually or electrically, by an interrogator device. The interrogator device will measure cardiac output and determine cardiac activity as a function of the electrode or electrodes used. A plurality of electrodes on an intravascular catheter will allow the surgeon to determine which electrode or electrodes stimulate the vagus nerve to achieve maximum suppression of cardiac activity.

While the optimal number of wires can vary depending upon the circumstances, four, eight or twelve wires per basket provide symmetry. Each wire is an independent electrode, electrically exposed only on its outer service at the point where it makes contact with the wall of the internal jugular vein, trachea, or esophagus. The electrodes may be self-expanding or retractable as a group when the device is deployed.

The vagus nerve can be stimulated in a unipolar or bipolar fashion. An array of electrodes in the form of a basket, balloon or umbrella device can be used to stimulate the vagus nerve between a chosen electrode rib and a separate ground, or between two chosen electrode ribs on the same device. This applies the basket, balloon or umbrella devices, whether with strips of foil, wires or umbrella tip electrodes, and regardless of whether the strip or wire electrodes are oriented longitudinally, transversely or spirally. For unipolar excitation, the ground can be an adhesive pad fixed to the patient's skin, either overlaying the vagus nerve or placed elsewhere.

The vagus nerve may be most effectively and easily stimulated with a single basket or balloon or steerable wire device in the internal jugular vein, esophagus or trachea. Alternatively, a bipolar electric field may be used that is preferably, but not limited to, between electrodes on individual devices in separate anatomical structures. For example, a balloon, basket or umbrella

catheter may be in the internal jugular vein, while another electrode is on a balloon, basket or umbrella in the trachea or in the esophagus.

Endotracheal and endoesophageal balloons, umbrellas or basket electrodes can be fitted on standard endotracheal or nasogastric tubes and nasogastric tubes. In the balloon device, electrically conductive electrodes can be oriented longitudinally, circumferentially, or helically, relative to the longitudinal axis of the anatomical feature in which the electrode device is implanted. In either longitudinal or circumferential embodiments, electrically active strips can be continuous or interrupted. In the case of interrupted strips, each segment of the strip can be an independent electrode.

Any two independent electrodes can be used in a bipolar fashion. Each independent electrode is an option recognized by a logic and control software of a multi-channel control box device. In the case of catheters bearing balloon, basket, or umbrella electrodes, two electrodes on catheters in distinct anatomical structures can be inflated or deployed adjacent to each other. This arrangement will gently place the vagus nerve between two electrode strips, and capturing the vagus nerve with the smallest possible effective voltage.

The optimum electric field may be between two electrically independent strips of a single catheter device in a single anatomic structure such as, but not limited to, the internal jugular vein. Alternatively, and depending on individual patient variability, it may be that optimal pacing is achieved between strips on two different catheter devices, each in a different anatomical structure. Such paired locations for the electrodes would include. but is not limited to, the jugular vein and esophagus, jugular vein and trachea or the esophagus and trachea. In each of these embodiments, the catheter devices are preferably positioned by the surgeon following ultrasound guidance, direct palpation, measurements of catheter insertion length, or any combination thereof. Fluoroscopy and echocardiography are alternative technologies that can be applied to confirm positioning.

At least one electrode can be applied directly to a surgically exposed vagus nerve. Thoroscopy, thoracotomy, or sternotomy can access the nerve itself. The present invention provides electrode devices that may be directly attached to the vagus nerve with greatly reduced mechanical damage to the neural tissue. This represents a significant advantage since repositioning of the electrode and therefore repeated clamping to the nerve may be necessary to determine the optimum location for electrical induction of asystole.

Direct placement of an electrode onto a vagus nerve can be by a clip means that carries at least one electrode, or a cuff means that completely or partially envelopes the nerve. The cuff may comprise solely an electrode means or the at least one electrode that is held against the nerve by the cuff means. The electrodes are comprised of material that is compressible or otherwise shaped to avoid indenting or crushing the neural tissue.

An entirely cutaneous array of adhesive electrodes can alternatively be used to create an electric field that would "capture" and stimulate the vagus nerve. Such an array can consist of, but is not limited to, an adhesive pad with from 1 to about 100 electrically independent skin electrodes, each isolated from the others and electrically connected to a multi-channel connector or hub. A single selected electrode from an array can be used for unipolar stimulation. Alternatively, they may be employed in pairs or other multipolar electrode combinations, or in combination with at least one other electrode positioned in the internal jugular vein, trachea or esophagus for bipolar stimulation.

The methods of the present invention introduce an electrode to a vagus nerve and thereby apply an electrical stimulation that results in a transient cardiac quiescence. The electrode device may be repositioned by the surgeon to a more advantageous location resulting in a greater desired cardiac response. Alternatively, one or more of the electrodes of the device may transmit an electric pulse to the nerve. The apparatus of the present invention will self-determine the preferred electrical charge to apply and to which electrodes. The method of the present invention will further comprise administering a pharmaceutical composition that will suppress escape of the heart from asystole. This will relieve the surgeon of concern that the quiescent heart will re-enter brachycardia or full beat while in the midst of a surgical procedure such as the suturing of an anastomosis between a bypass graft and a coronary artery.

The present invention is further illustrated by the following examples, which are not to be construed in any way as imposing limitation upon the scope thereof. On the contrary, it is to be clearly understood that resort may be had to various other embodiments, modifications and equivalents, thereof, which, after reading the description herein, may suggest themselves to those skilled in the art without departing from the spirit of the present invention.

Vagal Nerve Stimulator Apparatus.

The present invention, as shown in Figure 1, provides a multi-channel interrogator device box **10** that is microprocessor based and includes logic and control software to interrogate the closest electrode or electrode pairs to the vagus nerve "blindly" and automatically. This electronic device receives continuous input from a cardiac monitoring device **20** operably connected to a patient by a connection means **21**. The device can then sample the induced cardiac response resulting from an electric pulse applied to a particular electrode **30** or electrode pair **31** and thereby identify the electrode **30** or electrode pair **31** that are the most effective in producing Controlled Intermittent Asystole. Thus, the surgeon and anesthesiologist can be relieved of the necessity of physically locating the vagus nerve, as well as having to directly map the stimulation.

The multi-channel interrogator device box **10** automatically selects the most appropriate electrode or electrodes of an array of electrodes as a function of the cardiac output response. Although the logic and control software, however, is conceived to automatically interrogate the available electrode combinations, it is important that this multi-channel apparatus also be able to selectively function in a manual mode. The apparatus will, therefore, have a display, a plurality of numeric keys and knob dials **11**, a vagus nerve stimulation switch, and a vagus nerve destimulation switch, that can independently access the various electrodes electrically connected to a patient, such that an electrode **30** or electrode combination **31** can be manually selected.

The apparatus of the present invention further comprises a pulse generator **40** such as, but not limited to, GRASS™ nerve stimulator units. Such an electrostimulator includes, but is not limited to, a regulated power source, such as a battery and regulator, a nerve stimulation timer circuit, a nerve destimulation timer circuit, and a power amplifier(s). The type and quantity of timer circuits and power amplifiers can be chosen from any known to one of skill in the art.

The apparatus of the present invention offers a wide variety of unipolar or bipolar outputs **41**. The pulse generator **40** allows the duration of impulse to be controlled by a foot switch **50**. Impulse parameters can be varied either manually or automatically. Available frequencies can range between about 1 Hz and about 500 Hz. Preferred pulse amplitudes are in the range from about 0.1 volt to about 100 volts, with amperage of from about 0.05 mA to about 50 mA.

The apparatus of the present invention further comprises a cardiac pacer device **60** for pacing the heart out of asystole and a pacer-to-patient

connecting means **61**. In a preferred embodiment the cardiac pacer **60** is electrically connected to the logic and control circuit and associated software so that it is integrated with the pulse generator for vagal nerve stimulation.

The vagal nerve stimulator output can be slaved to the cardiac pacemaker, which can have parameters similar to those of presently available pacer devices. The cardiac pacer output can be "off" whenever the vagal stimulator output is "on". The software controlling the cardiac pacer and vagal stimulator can automatically commence cardiac pacing if the heart does not resume beating within a pre-determined interval from cessation of vagal nerve electrostimulation. This feedback mechanism provides a significant safety feature when CIA is used clinically.

In another preferred embodiment of the present invention, a foot pedal assembly **50** can activate the vagus nerve stimulator. A foot pedal assembly **50** has a normally open heart stimulation foot switch and a heart destimulation foot switch that can be used as an alternative to either automatic or hand-operated switches. The provision of a foot pedal assembly **50** permits the surgeon to control when the heart and vagus nerve stimulation and destimulation occur while leaving the hands free to perform other procedures. This also permits the surgeon's hands to remain sterile, since contact with the housing or switches is avoided. The foot pedal assembly **50** is connected via cable or other means to an electronic control device within the housing.

During open chest surgery or minimally invasive surgery, the foot switch is pressed to selectively initiate or stop the heart beat as required. The heart may be stimulated either through the present device to beat for a predetermined time to permit blood flow throughout the body and then again be electrostimulated via the vagus nerve for asystole and allow the surgeon to continue stitching. An alternative to providing two different foot pedal assemblies **50** would be to provide a single foot switch with intermittent switches between stimulation and destimulation each time the switch is actuated. It is also contemplated that automatic stimulation by means of a cardiac pacer device could be provided after a preset time period.

In yet another embodiment of the invention, a voice-activated switch can be used that incorporates commercially available voice-recognition software into a verbal control mechanism to turn the vagal nerve stimulator on and off. This switch can also function in a "slaved" fashion, such that whenever the vagus nerve stimulator is turned on, output from the cardiac pacemaker is

turned off. While these hardware devices are modifications of presently available devices, they would be customized and combined into a single unit for this new application of producing controlled intermittent asystole.

Intravascular Catheter Electrode.

The present invention provides intravenous catheters having a distally disposed electrode means that can be expanded in the internal jugular vein so as to press up against the internal wall of the internal jugular vein and force contact between an electrode and the blood vessel wall. This allows electric current and electric fields to pass through the thin wall of the internal jugular vein to stimulate the vagus nerve, which lies immediately adjacent to the internal jugular vein. The electrode means can be added to any intravascular catheter device known to one of skill in the art including, but not limited to, the Swan Ganz catheter, the tip of which would aid in proper catheter positioning and monitoring of pulmonary artery pressures. The catheter itself can also have one or move intravenous port(s) for administration of fluids and drugs, with appropriate intravenous access hubs. The electrical access to the electrode means can be provided via an external multi-channel electric plug connector.

The intravenous catheters can be steerable catheters that allow precise positioning of an electrode means close to the vagus nerve, thereby minimizing the electrical energy needed to "capture" the nerve and induce Controlled Intermittent Asystole. It is thereby possible to "map" the location of the vagus nerve by determining the feedback signal derived from the cardiac output monitor in response to nerve stimulation.

The present invention, as shown in Figures 2A and 2B, provides an intravascular catheter device for delivering an electric pulse to a nerve. The catheter device comprises a shaft **100** having a distal region **110** and a proximal region **120**, the distal region **110** having an expandable electrode means **200** and an electrode expanding means **300**. The shaft **100** may include a means of supplying an electrical pulse **130** to the expandable electrode means **200**. The means of supplying an electrical pulse **130** are in electrical contact with a multi-channel connector means **131**. The electrical pulse supply means **130** also has a hub **132** attached thereon to hold the supply means **130** firmly. The shaft **100** may further comprise a handle **101** and a transcutaneous sheath **102**. The intravascular catheter can be inserted though said sheath **102**, which can be sutured to a patient's skin near the site of insertion. There can be a valve on said

sheath to avoid bleeding, and the catheter can be rotatable within the transcutaneous sheath **102**. While not wishing to limit the invention, the preferable means of supplying an electrical pulse **130** to an electrode **200** is a wire.

Although it is contemplated that the dimensions of the expandable electrode means **200** will be selected as a function of the blood vessel or other anatomical structure receiving the catheter, and where the catheter is inserted into the recipient human or animal, in preferred embodiments of the electrode, the length of the electrode will be between about 1 cm and 15 cm, most preferably between about 2 cm and 6 cm. The diameter of the shaft is preferably between about 0.5 and 5 mm, most preferably 1 mm.

The preferred length of the intravascular catheter is dependent upon the point of insertion of the catheter into a human or animal. When the catheter is inserted in the neck, the length of the shaft **100** is between about 15 cm and 30 cm, preferably between about 15 cm and 25 cm. For subclavian insertion of a catheter, the preferred length of the shaft **100** is between about 20 cm and 40 cm, most preferably between about 25 cm and 35 cm. For femoral insertion of the catheter, the preferred length of the shaft **100** is between about 50 cm and about 120 cm, most preferably between about 80 cm and about 100 cm. For atrial insertion, wherein the catheter electrode device is advanced from the cardiac atrium into the superior vena cava or internal jugular vein, the preferred length is between about 5 cm and about 25 cm, most preferably between about 10 cm and 15 cm.

(i) Catheter Wire or Basket Electrode. The expanding electrode means **200** shown in Figure 2A is selected from a variety of patterns and shapes that resemble, but are not necessarily limited to, the ribs or staves of a barrel, as shown in Figures 3A-3D. The electrode means are electrically independent of each other.

A preferred embodiment of the expandable electrode means **200** and the electrode expanding means **300** is shown in Figure 3A, wherein the electrode means **200** is a basket catheter electrode with at least one expandable rib **201**. In a preferred embodiment, the expandable rib **201** or plurality of such ribs are electrically conductive wires. Thin wires are preferred with a thickness of between about 1/128 inch and 1/8 inch, most preferably between about 1/64 and 1/16 inch. In another preferred embodiment, the expandable ribs **201** are electrically conductive strips from about 1/128 inch to about 1/4 inch wide, most

preferably from about 1/64 inch to 1/4 inch. In yet another preferred embodiment the expandable ribs **201** are electrically non-conductive strips with electrodes dispersed thereon. In a most preferred embodiment, the electrically conductive wire or strip is comprised of a proximal region **202**, a central region **203** and a distal region **204**, wherein the proximal region **202** and the central region **203** form a first angle and the central region **203** and the distal region **204** form a second angle. Preferably the first and second angles are between about 1° and about 180°. Most preferably, the first and second angles are between about 90° and about 120°.

Preferably, the ribs **201** are between 1 and about 48 in number, more preferably between 2 and about 12 in number. In a preferred embodiment, the length of the expanded electrode **200** is between about 1 and about 15 cm. More preferably, the length is between about 2 and about 6 cm. The diameter of the catheter before expansion is the diameter of the catheter shaft **200** and is 0.5 mm to about 5 mm, most preferably 1 mm.

In one embodiment of the present invention, the central region **203** is electrically exposed, and the proximal region **202** and distal region **204** are electrically insulated. In this embodiment, the length of electrically exposed central region **203** is between 0.1 cm and about 10 cm, most preferably between 0.5 and about 5 cm. The means of applying an electrical pulse **130** are preferably, but not limited to, wires electrically connected to the expandable ribs **201**. The wires **130** are electrically independent of one another, and pass through the shaft **100.** The wires **130** and are electrically connected to a multi-channel electrical connection **131**, as shown in Figure 2A. The electrode expanding means of the preferred embodiment is a rod **300** capable of sliding within a lumen **150** of the shaft **100**. The rod **300** has a distal end **301**. The expandable ribs **201** are attached to the distal end **301** of the rod **300**.

In another embodiment of the present invention, shown in Figure 3B, the expandable ribs **201** are arcuate when expanded. In a preferred embodiment, the length of an electrically exposed central region **203** of the expanded arcuate electrode is between about 0.1 cm and about 2.5 cm. More preferably, the range is between 0.5 cm and 2.0 cm.

The present invention is intended to include other forms of the expandable electrode such as, but not limited to, electrodes **206** circumferentially disposed coaxially around the rod **300**, shown in Figure 3C, a helix as shown in Figure 3D. In the circumferential electrode embodiment shown in Figure 3C,

non-conductive ribs **205** support electrically exposed electrodes **206** circumferentially disposed thereon. Each circular electrode **206** is electrically connected to an electric pulse applying means **207** and a multi-channel electrical connection **131**, as shown in Figure 2A.

The expandable catheter electrodes may be deployed, once the catheter has been implanted in the blood vessel and placed by the surgeon in the proximity of a vagus nerve. Expansion is by retracting the shaft **100** relative to the distal end **301** of the rod **300**. This exposes the self-expanding electrode means **200** that were disposed against the rod **300** within the lumen **150** of the shaft **100**. In another embodiment, the cathode means **200** can be fixed to the tip **301** and to the distal end **110** of the catheter shaft **100**. In this embodiment, partial retraction of the rod **300** into the lumen **150** of shaft **100** will force the electrode means **200** to expand outwards. The electrode means **200** are stretched when the rod **300** is extended relative to the distal end **110** of the shaft **100**, thereby reducing the diameter of the rod **300** and electrode **200**, to facilitate catheter electrode insertion into, or removal from, an anatomical structure. Alternative means of deployment of the electrode means **200** and expansion thereof are contemplated by the present invention including, but not limited to, extending the rod **300** from the shaft **100**, and rotating the rod **300** so that a helical electrode means **208**, such as shown in Figure 3D, may expand outwards.

In yet another embodiment of the catheter electrode device contemplated by the present invention, shown in Figure 3E, the expanding means is a shape memory implanted in the conductive material of the expandable electrode **201**. The expanded shape of the electrode is pre-selected and implanted in the conductive material of the electrode means **201** by methods known to those of skill in the art. The shape of the preferred embodiment of the expanded electrode includes, but is not limited to, the angular shape of Figure 3E, arcuate ribs, a helix or any other shape that will provide electrical contact between the catheter electrode **201** and the interior wall of a blood vessel or any other anatomical structure. The electrode means will expand spontaneously when the shaft **100** of the catheter device is retracted relative to the electrode. A shape memory electrode may also include a rod **300** to aid in the retraction of said shaft **100** by preserving the length of the electrode means **201** as shaft retraction occurs.

(ii)Catheter Balloon Electrode. An electrode expansion means of the present invention is contemplated to be an inflatable balloon having electrically

conductive wires or continuous or discontinuous strips thereon. Once a catheter electrode device is implanted in a blood vessel (or trachea or esophagus) the balloon is inflated with gas or liquid so as to make electrical contact between the electrode and the interior wall of the blood vessel.

The metal foil strips or wires on the balloon can be oriented relative to the long axis of the catheter device in any fashion that include longitudinal, circumferential, helical or arcuate ribs, or any other shape that will provide electrical contact between the catheter electrode **201** and the interior wall of a blood vessel or any other anatomical structure, and would be electrically isolated from each other. As with the basket wire electrodes described in (i) above, the electrodes are individually accessible from the hub of the catheter. Wire electrodes may be used as described for the basket array, with the expandable balloon pressing the electrically naked region of the wires against the interior wall of a blood vessel. Areas of the wires which do not make contact with the tissue walls may be, but not necessarily, insulated.

The expandable balloon is comprised of any expandable material known to one of skill in the art such as, but not limited to, latex, plastic, polymer or monomer that is acceptable for implanting into a human or animal. The balloon **400** may be comprised of a flexible metallic foil electrically connected to a means of applying an electric pulse **207**, so that the surface of the balloon can function as an expandable electrode. In one embodiment, the balloon **400** comprises a flexible metallic foil with an insulating strip imposed thereon or a plurality of insulating layers, thereby forming a balloon having multiple electrodes electrically connected to a means of applying an electric pulse **207**. Alternatively, the balloon **400** may be comprised of alternate strips of metallic foil and insulating material, each foil strip individually electrically connected to a means of applying an electric pulse **207**

The balloon is selected from a variety of shapes including, but not limited to, an ovoid or spherical balloon located at the distal end of a catheter or tube. The balloon may encircle, in whole or in part, a catheter or a tube, thereby forming a collar. A collar balloon may be selected from a variety of shapes including, but not limited to, an oval, a cylinder, or any other form known to one of ordinary skill in the art.

The balloon may be of any length and diameter when expanded that will establish contact between the balloon and the interior wall of an anatomical structure. Preferably, the dimensions of the expanded balloon **400**

will be such that the balloon **400** cannot cause physical trauma to said structure. The preferred length of the balloon is between about 1 cm and 10 cm, most preferably between about 2 cm and 8 cm. The preferred diameter of the expanded balloon is between about 1 cm and 8 cm, most preferably between about 2 cm and 6 cm.

For transvenous stimulation of the vagus nerve with an electrode mounted on a balloon, a delivery catheter may be used that is multiply fenestrated proximally and distally to the balloon, thereby avoiding total obstruction of blood flow. The balloon expansion means of the present invention offers the additional advantage that the balloon may have a preselected shape incorporating at least one, or a plurality of, grooves, notches, traversing tubes or tunnels, or any other form. Such indentations or traversing means of communication allow unobstructed blood flow while still maintaining contact between the expandable electrode and the interior wall of the blood vessel. Preferably the ridges number between 1 and 20, more preferably 1 and 12, and most preferably between 2 and 6 in number. When the balloon incorporates ridges, and the accompanying indentations, the electrode or plurality of electrodes are disposed on said ridges. While the present invention contemplates from 1 to about 10 electrodes on a ridge, the preferred number is from 1 to 5. The means to inflate a balloon may be within a catheter or tube or disposed on the exterior surface of said catheter or tube, and connected to a means to introduce a gas or liquid to inflate the balloon once the surgeon has placed the balloon electrode adjacent to a target nerve.

In one embodiment of the present invention, shown in Figure 4A, the catheter electrode device, the device comprises at least one expandable electrode **201** longitudinally dispersed on an expandable balloon **400** at the distal end of the catheter shaft **100**. In another embodiment, shown in Figure 4B, the electrodes **206** are circumferential and are electrically connected to electric pulse applying means **207**. In yet another embodiment, shown in Figure 4C, the electrode **208** is helically arranged coaxially to the inflatable balloon **400** and the electrode is electrically connected to a means of supplying an electric pulse **207**.

In a preferred embodiment of the present invention as shown in Figure 4D and in cross-section Figure 4E, the balloon **400** includes at least one raised rib **401**, with an expandable electrode **201** exposed thereon, and wherein the expanded balloon is non-obstructive to the blood flow. The present invention contemplates that the inflatable balloon may have a plurality of raised ribs with

electrode means thereon, and that the raised ribs may be, but not limited to, longitudinal, circumferential, or helical arrangements.

In yet another embodiment of the catheter balloon electrode device, the expandable electrode means **201** is a flexible wire mesh, or a metal foil that partially, substantially or completely covers the surface of the balloon **400**. The present invention further contemplates that the expanding electrode means **201** may be any other flexible conductive material that will allow an electric pulse or field to be applied to a nerve.

In a preferred embodiment of the catheter balloon device, the expandable electrode means **201** may be from 1 to about 50 in number, most preferably 1 to 24 in number. The electrodes **201**, when a plurality, are electrically isolated from each other. In the preferred embodiments, the expandable electrodes **201** are individually connected to a means of applying an electrical pulse that is connected to a multi-channel plug connector.

In embodiments of the catheter device, having an inflatable balloon, shown in Figure 4F, the electrode **201** or plurality of electrodes are attached to the balloon so that when the balloon is inflated, the electrodes have a pre-selected arrangement. In a further embodiment, the electrodes **201** are not fixed to the inflatable balloon **400** but held in a pre-selected arrangement by means of at least one connecting, non-electrically conductive yoke **402** attached to the electrodes **201**.

(iii) Catheter Umbrella Electrode. The present invention provides a catheter umbrella electrode means, as shown in Figures 5A and 5B. The umbrella electrode means comprises at least one, and preferably a plurality of, expandable electrode means, wherein each electrode **600** is mounted on a spoke **601** and electrically connected to a means of delivering an electric pulse **605** to the electrode **600**, and wherein said means **605** comprises wires. The electrodes **600** may be, but not necessarily, disposed at the distal ends **602** of said spokes **601**, The spokes **601** are composed of any electrically conductive or non-conductive material known to one of skill in the art. The spokes **601** include, but are not limited to, wires, strips or any other suitable form known to one skilled in the art. When electrically conductive, the spoke **601** comprises the means of delivering an electric pulse **605** and is coated with a non-conductive material. Individual spokes of a plurality of spokes are electrically isolated from all others. The expandable electrodes **600** are deployed in the fashion of an umbrella to contact the electrically exposed electrodes **600** of the umbrella spokes against the

wall of a blood vessel or other anatomical feature. The umbrella spokes serve the same function as the ribs of the basket-type device shown in Figures 3A, 3B and 3E. Preferably, the spokes **601** number between 1 and about 50, more preferably between 4 and about 24.

One embodiment of the catheter umbrella electrode device, shown in Figure 5A, has a shaft **100** with a lumen **150** and a rod **300** disposed therein and an umbrella electrode means. Said rod **300** has a distal end **301** with one, or a plurality of radially disposable spokes **601** attached thereto. The spokes **601** are able to move radially away from the rigid rod and thereby contact the interior wall of a blood vessel or other anatomical feature.

A slideable collar **603**, coaxially disposed on the rod **300** is connected to the plurality of radially disposed spokes **601** by a plurality of connecting means. The connecting means comprises a linking wire **604** pivotally joined to the slideable collar **603** and to a spoke **601**, one linking wire **604** attached to each spoke **601**.

In another embodiment of the catheter umbrella electrode device, shown in Figure 5B, the slideable collar **603** is pivotally attached to the plurality of spokes **601**. Linking wires **604** are pivotally joined to the distal end **301** of the rod **300** and to the spokes **601**. The shaft **100** may be positioned so that it overlays the wires or strips to form a protective sheath. In one embodiment, linking wires **604** can comprise the means of delivering an electric pulse **605**.

By retracting the slideable collar **603** relative to the rod **300**. The radially disposed spokes **601** are positioned parallel to the longitudinal axis of the rod **300**. Wires **605** attached to the electrodes **600** may also be attached to the slideable collar **603** and used to retract or extend the collar **603** relative to the rod 300.

By retracting the rod **300** into the lumen **150** of the shaft **100**, the shaft becomes a protective sheath around the spokes **601** so that the catheter may be implanted in a blood vessel or other anatomical structure without the electrodes **600** penetrating or otherwise injuring the wall of said structure.

When the surgeon has implanted the catheter adjacent to the vagus nerve, the rod **300** is extended to remove the spokes **601** and the electrodes **600** from the lumen **150** of the shaft **100** comprising the protective sheath, and the slideable collar **603** is positioned relative to the rod **300** so that the spokes **601** extend away from the rod **300**, and the electrodes make electrical contact with the wall of the blood vessel or other anatomical structure.

Neural Clip Electrode. After direct surgical exposure of the vagus nerve, an electrode means electrically connected to a pulse supply means can be placed in direct contact with the exterior surface of the nerve. Stimulation of the vagus nerve can be achieved by direct access to the vagus nerve through either a neck incision or via thoracoscopy, thoracotomy or through a sternotomy. The vagus nerve can be approached lateral to the pericardium and below the level of the right innominate artery to avoid the right recurrent laryngeal nerve. This can be accomplished thoracoscopically without the necessity of a formal sternotomy or neck incision.

The present invention provides clip electrode means, shown in Figures 6A-6C, for directly contacting an electrode means with a nerve, comprising a first electrically non-conductive member **700** pivotally secured by a pivot means **701** to a second electrically non-conductive member **702** to form confronting yaws. In one embodiment, an electrode **703**, electrically connected to a means for applying an electric pulse **704** to said electrode **703**, is attached to the first electrically non-conductive member **700** and in the confronting jaw region thereof. In another embodiment of the present invention, opposing electrodes are disposed on the electrically non-conductive members, **700** and **702** within the confronting jaw region.

The present invention reduces crush trauma to a nerve by the electrodes being compressible electrically conductive material that cushions the nerve tissue, as shown in Figure 6A. In yet another embodiment of the clip electrode, at least one electrically non-conductive member has a groove **705**, shown in Figures 6B and 6C, wherein the groove **705** is lined with an electrode.

In all embodiments of the present invention, the electrode may be, but is not limited to, a concave form as shown in Figures 6B and 6C, a compressible electrically conductive material that cushions the nerve tissue, a wire, a strip, a wire mesh or wire wool, or any other conductive material or form that will not induce physical trauma to the neural tissue. In another embodiment, opposing grooves are in each non-conductive member **700** and **702**. In all embodiments, the preferred means for applying an electric pulse **704** to an electrode **703** is a wire electrically connected to a multi-channel connector **706**.

In yet another embodiment the clip electrode has at least two electrodes **703**, electrically isolated from each other, as shown in Figure 6D. Each electrode **703** can be independently electrically connected to a separate

means of supplying an electric pulse. Thus, the electric pulse may be delivered to the nerve between at least two electrodes **703** on opposing electrically nonconductive members **700** and **702**, as shown in Figure 6C, or on one electrically nonconductive member as shown in Figure 6D.

Neural Cuff Electrode. The present invention further provides a cuff device, shown in Figures 7A and 7B, for the direct application of an electrode to a nerve. In one embodiment, the cuff device is a flexible or malleable wire mesh **800** capable of conforming to the surface of the nerve **801**, as shown in Figure 7A. In another embodiment, the cuff device is an electrically conductive sheet that can partially or completely envelop a nerve. In both embodiments, the electrode has a means **802** to electrically connect the electrode to a pulse generator. In either embodiment, the surface of the electrode in contact with the nerve is electrically exposed, while the opposite surface of the electrode is, but not necessarily, electrically insulated to avoid electrical stimulation of adjacent anatomical structures.

In another embodiment of the cuff device, as shown in Figures 7B and 7C, the cuff device has an electrically nonconductive member **803** having a traversing channel **804** and at least one electrode **805** and a means of applying an electric pulse **802** to said electrode **805** therein. In the most preferred embodiment, the electrode **805** is a wire mesh. In another preferred embodiment, the electrode **805** is a conductive sheet. In yet another preferred embodiment, such as shown in Figure 7D, the cuff device has a first electrode **806** and a second electrode **807**, wherein the electrodes are electrically isolated from each other, and each electrode is electrically connected to a separate means of applying an electric pulse **802**.

Transdermal Array Electrode. The present invention provides electrode arrays supported by a non-conductive support means such as, but not limited to, a pad. The pad can be adhesive and can be applied to the surface of the skin so that the array of electrodes is in electrical contact thereon. To increase electrical conductivity between the electrodes and the skin, an intervening conductive gel, known to one of skill in the art, can be included. The cutaneous electrode array can be placed on or around the neck in the vicinity of the vagus nerve. When placed around the neck, the non-conductive support may include a Velcro strap

or any other fastening device to secure the pad to the patient. The pad can be shaped to accommodate the neck region of the patient.

The transcutaneous electrode array may be used to provide a unipolar electrode, wherein a second catheter electrode is implanted in the patient adjacent to the nerve to be stimulated. An electric pulse is applied to an individual electrode of the array of electrodes and the implanted catheter electrode is grounded. Alternatively, the electric pulse is applied to the implanted catheter electrode, and one or more of the array electrodes is grounded.

The transcutaneous electrode array provided by the present invention may also be used to apply a bipolar electric pulse to a nerve, wherein the anode and cathode electrodes are selected from the electrodes of the array. Connection to the vagus nerve stimulation device allows the interrogatory unit therein to selectively determine the optimum pair of electrodes to achieve maximum stimulation of the target nerve, most preferably the vagus nerve. The present invention also provides an electrode array device, such as shown in Figures 8A-C for delivering an electric pulse through the skin to a nerve. The electrode array device comprises an electrically non-conductive support **900** having a plurality of electrodes **901**, wherein said electrodes **901** are electrically isolated from each other. Each electrode **901** is connected to a means of supplying an electric pulse **902**, wherein said means **902** is a wire and the plurality of wires are electrically connected at their proximal ends to a multi-channel connector **903**. The electrically non-conductive support **900** may be, but is not limited to, a sheet, a pad, a block such as a cube or a cylinder, and may be any geometric form such as, but not only, a square, oblong, broad strip, circular or ovoid disc.

In one preferred embodiment, as shown in Figure 8A, the electrically non-conductive support **900** is a sheet and the array of electrodes **901** are exposed on one face of said sheet. Each electrode **901** is connected to a means of supplying an electric pulse **902**, wherein said means **902** is a wire and the plurality of wires are electrically connected at their proximal ends to a multi-channel connector **903**. In another preferred embodiment of the electrode array device of the present invention, the means of applying an electric pulse **802**, shown in Figure 8B, is a sheet with a traversing hole **904**. In yet another embodiment, as in Figure 8C, a means of communication **905** connects the traversing hole **904** to the outer edge **906** of the electrically non-conductive support **900**. This connecting means may be, but is not limited to a slit, a slot, or

a channel. The communication means **905** and traversing hole **904** are intended to allow easy placement of an electrode on a patient's neck.

In another preferred embodiment, as shown in Figure 8D, the electrically non-conductive support **900** is in a necklace-like configuration and the array of electrodes are exposed on one face thereof. A In another preferred embodiment, as shown in Figure 8E, the electrically non-conductive support **900** is in a turtleneck-like configuration and the array of electrodes are exposed on one face thereof. Each electrode **901** is connected to a means of supplying an electric pulse **902**, wherein said means **902** is a wire and the plurality of wires are electrically connected at their proximal ends to a multi-channel connector **903**.

In each of the embodiments shown in Figs 8A-8E, the electrodes may be in a variety of shapes, such as circular, square or elongated. Furthermore, the electrode array can have fasteners **907** such as, but not limited to, Velcro, straps or buckles, that will allow the non-conductive support to be secured to a human or animal. Alternatively, the invention provides that an inflatable collar can be positioned on each of the embodiments shown in Figs 8A-8E, that will allow the non-conductive support to be secured to a human or animal.

In all embodiments of the Transdermal Array Electrode, it is anticipated that the width of the non-conductive support **900** will be between about 1.5 cm and about 10 cm, preferably between about 2 cm and about 5 cm. It is anticipated that the length of the non-conductive support **900** will be between about 1 cm and about 10 cm, preferably between about 2 cm and about 5 cm. In the case of the necklace configuration, this length of the non-conductive support is between about 15 cm and about 45 cm. It is further anticipated that the depth of the non-conductive support **900** will be between about 0.1 cm and about 3 cm, preferably between about 0.2 cm and about 1.5 cm.

Another embodiment of the cutaneous array electrode is a single electrode applied to the surface of the skin. In yet another embodiment, a plurality of electrodes in an array can be electrically connected to act as a single electrode. The electrode array device of the present invention may have an optional electrically conductive gel layer and an optional electrically conductive adhesive layer to increase the efficiency of electrical contact with the skin.

Endotracheal and Nasogastric Tube Electrodes. The present invention contemplates embodiments of the balloon, basket, umbrella and steerable devices as described above, combined with endotracheal tubes used for maintaining ventilation during general anesthesia, or with a nasogastric or esophageal tube used for gastric decompression. While the sizes of the expandable basket or umbrella electrode devices used in conjunction with endotracheal or nasogastric tubes are adapted for use in the trachea or esophagus, the concepts and designs are similar.

One approach to the stimulation of the vagus nerve is to access the internal jugular vein with a catheter electrode. The internal jugular vein runs parallel to, and is intimately associated with, the vagus nerve along the length of the vein in the neck of humans. The trachea and esophagus, however, also lie in close proximity to the vagus nerve in humans. These anatomical structures are ideally suited for the location of catheter or tube electrodes useful for stimulating the vagus nerve. By accessing the trachea or the esophagus, there is no requirement for a neck incision to insert an intravascular catheter or direct surgical isolation of the vagus nerve. Tracheal or esophageal electrodes may be combined with a cutaneous electrode device to provide unipolar neural electrostimulation. Several different devices of the present invention utilize these alternative and less invasive routes.

The present invention further provides an endotracheal or nasogastric tube electrode device, as shown in Figure 9A, comprising an endotracheal or nasogastric tube **1000** having an inflatable collar **1001** which may be, but is not limited to, a balloon design, and a means to inflate **1002** said collar **1001**, at least one expandable electrode means **1003** on said collar **1001**. The electrode means **1003** is so positioned that when the collar **1001** is inflated the electrode means **1003** is in contact with the interior lining of the trachea. The electrode means **1003** is electrically connected to a means of supplying an electric pulse **1004** and a multi-channel connector means **1005**.

The electrode expansion means **1001** should not be construed as being only an inflatable collar. The present invention contemplates using a balloon, umbrella, barrel or basket electrode. The present invention provides a catheter umbrella electrode means, as shown in Figure 9B. The umbrella electrode means comprises at least one, and preferably a plurality of, expandable electrodes **1007**, each electrode **1007** mounted on a spoke **1008** and electrically connected to a means of supplying an electric pulse **1009** to the electrodes **1007**,

wherein the electrodes **1007** are disposed at the distal ends **1010** of said spokes **1008**, and wherein said means **1009** comprises wires. The spokes **1008** are composed of an electrically conductive or non-conductive material. The spokes **1008** are, but not limited to, wires, strips or any other suitable form known to one skilled in the art. When electrically conductive, the spokes **1008** are coated with a non-conductive material. Each spoke is electrically isolated from all others. The expandable electrodes **1007** are deployed in the fashion of an umbrella to contact the electrically naked tips of the umbrella spokes against the wall of a blood vessel or other anatomical feature.

One embodiment of the endotracheal or nasogastric tube umbrella electrode device, shown in Figure 9B, has an endotracheal or nasogastric tube **1000**, and a plurality of radially disposable spokes **1008** attached thereto. The spokes **1008** are able to move radially away from the rigid rod and thereby contact the interior wall of the trachea.

A slideable collar **1011**, coaxially disposed on the endotracheal or nasogastric tube **1000** is connected to the plurality of radially disposed spokes **1008** by a plurality of connecting means. The connecting means comprises a linking wire **1012** pivotally joined to the slideable collar **1011** and to a spoke **1008**, one linking wire **1012** attached to each spoke **1008**.

By retracting the slideable collar **1011** relative to the region of the endotracheal or nasogastric tube **1000** in the patient, the radially disposed spokes **1008** are positioned parallel to the longitudinal axis of the tube **1000**. Wires **1009** attached to the electrodes **1007** may also be attached to the slideable collar **1011** and used to retract or extend the collar **1011** relative to the tube **1000**.

When the surgeon has inserted the endotracheal or nasogastric tube **1000** in the trachea adjacent to the vagus nerve, the slideable collar **1011** is positioned relative to the tube **1000** so that the spokes **1008** extend away from the tube **1000**, and the electrodes **1007** make electrical contact with the wall of the blood vessel or other anatomical structure.

The electrodes may be arranged longitudinally relative to the central longitudinal axis of the endotracheal or nasogastric tube. The electrodes may be circumferentially arranged in a coaxial relationship with the tube **1000**. The electrodes may be spirally arranged around the inflatable balloon or collar. The inflatable collar may be inflated by the inflation means **1002** with air, gas or a liquid.

The present invention also provides an endotracheal or nasogastric tube **1000**, as shown in Figure 9C. This embodiment provides for expandable or rigid electrodes which are substantially embedded within the tube material to avoid living tissue irritation. The electrode means comprises at least one, and preferably a plurality of, electrodes **1003**, each electrode **1003** electrically connected to a means of supplying an electric pulse **1009** to the electrodes **1003**, wherein the electrodes **1003** are exposed to the exterior surface of the tube **1000** adjacent the distal end of said tube **1000**, and wherein said means **1009** comprises wires. The electrode means are electrically independent of each other.

A preferred embodiment of the expandable electrode means and the electrode expanding means wherein the electrode means is a basket catheter electrode with at least one expandable rib. In a preferred embodiment, the expandable rib or plurality of such ribs are electrically conductive wires. Thin wires are preferred with a thickness of between about 1/128 inch and 1/8 inch, most preferably between about 1/64 and 1/16 inch. In another preferred embodiment, the expandable ribs are electrically conductive strips from about 1/128 inch to about 1/4 inch wide, most preferably from about 1/64 inch to about 1/4 inch. In yet another preferred embodiment the expandable ribs are electrically non-conductive strips with electrodes dispersed thereon. In a most preferred embodiment, the electrically conductive wire or strip is comprised of a proximal region, a central region and a distal region, wherein the proximal region and the central region form a first angle and the central region and the distal region form a second angle. Preferably the first and second angles are between about 1° and about 180°. Most preferably, the first and second angles are between about 90° and about 120°.

Preferably, the ribs are between 1 and about 48 in number, more preferably between 2 and about 12 in number. In a preferred embodiment, the length of the expanded electrode is between about 1 and about 15 cm. More preferably, the length is between about 2 and about 6 cm. The diameter of the catheter before expansion is the diameter of the catheter shaft and is 0.5 mm to about 3 mm, most preferably 1 mm.

In one embodiment of the present invention, the central region is electrically exposed, and the proximal region and distal region are electrically insulated. In this embodiment, the length of electrically exposed central region is between 0.1 cm and about 10 cm, most preferably between 0.5 and about 5 cm. The means of applying an electrical pulse are preferably, but not limited to, wires

electrically connected to the expandable ribs. The wires are electrically independent of one another, and pass through the shaft. The wires and are electrically connected to a multi-channel electrical connection.

Method of inducing asystole by vagal electro-stimulation and CIA pharmaceutical composition treatment

The present invention provides a method for the induction of cardiac asystole by the application of an electric pulse or field to the vagus nerve. The CIA pharmaceutical composition provides a background pharmaceutical state wherein the impact of vagal nerve stimulation is potentiated and heart will not spontaneously escape from the electrically induced asystole. Throughout subsequent cardiac surgery, the surgeon monitors the heart function and can selectively reinitiate the heart beat by means of a cardiac pacer device, slaved to the vagal nerve stimulator. This can also be performed automatically if the heart beat fails to resume within a preset time period.

The present invention, therefore, provides a method of inducing and prolonging asystole by implanting a catheter or tube expanding electrode into a blood vessel, trachea, or esophagus of a human or animal or by applying a cutaneous electrode. The electrodes are positioned adjacent to the vagus nerve by the surgeon, and said electrodes are connected to the vagus nerve stimulator by means of multi-channel connectors and an output. At least one output from the stimulator is used, preferably two outputs, each connected to a separate electrode device.

The surgeon adjusts the vagal nerve stimulator to deliver a first unipolar or multipolar electric pulse to an implanted cutaneous electrode and the output of the heart is monitored by the microprocessor. Random selection of electrodes is then followed by additional pulses until a maximum state of asystole is achieved. The CIA pharmaceutic composition that comprises an acetylcholinesterase inhibitor, a β-adrenogenic receptor blocker and a calcium channel blocker, is administered before or after the initial testing. An electric pulse of optimum amplitude and frequency is applied to the previously selected electrode combination and controlled intermittent asystole, with minimal or no escape, results. Once the surgical procedure is completed, or predetermined point selected by the surgeon or preselected automatically by the vagus nerve stimulator, the heart is removed from asystole by a cardiac pacer means operated by the surgeon or by the vagus nerve stimulator.

The above description provides certain preferred embodiments of the devices and methods of the present invention. However, it is understood that many modifications and additional embodiments can be routinely made in view of the disclosure, and all such embodiments are intended to be encompassed within the spirit of the invention.

CLAIMS

We claim:

1. A catheter device for delivering an electric pulse to a nerve, comprising a distal region and a proximal region, said distal region having at least one expandable electrode and an electrode expanding means, said proximal region having an electrical connecting means for applying an electric pulse to the expandable electrode.

2. The catheter device of Claim 1, wherein the expandable electrode is longitudinally arranged.

3. The catheter device of Claim 1, wherein the expandable electrode is circumferentially arranged.

4. The catheter device of Claim 1, wherein the expandable electrode is spirally arranged.

5. The catheter device of Claim 1, having from 1-24 electrodes.

6. The catheter device of Claim 1, wherein the expandable electrode is an electrode selected from the group consisting of a wire, a basket, a strip, or a plurality of electrodes dispersed on an electrically non-conducting material.

7. The catheter device of Claim 1, wherein the expandable electrode comprises a proximal region, a central region and a distal region, and wherein when the electrode is expanded the proximal region and the central region form a first angle between about 1° and 180°, and the central region and the distal region form a second angle of between about 1° and 180°.

8. The catheter device of Claim 7, wherein the first and second angles are between about 90° and 180°.

9. The catheter device of Claim 7, wherein the expandable electrode, when expanded, has a total length of between 1.0 and 15 cm.

10. The catheter device of Claim 7, wherein the central region is between about 0.1 and 10 cm.

11. The catheter device of Claim 1, wherein the catheter has a lumen, and the electrode expanding means comprises a rod disposed within said lumen, and wherein the rod has a distal end connected to the expandable electrode so that the catheter forms a sheath over the expandable electrode means and the rod.

12. The catheter device of Claim 1, wherein the electrode expanding means comprises an inflatable balloon.

13. The catheter device of Claim 1, wherein the electrode expanding means comprises a metallic shape memory means.

14. The catheter device of Claim 1, wherein the expandable electrode means, when expanded is at least one arcuate electrode.

15. The catheter device of Claim 1, wherein the proximal end of the catheter has a handle and a hub, wherein the hub is connected to the means of applying an electric pulse to the expandable electrode.

16. The catheter device of Claim 12, wherein the balloon has at least one ridge thereon to allow the passage of fluid therearound, and wherein at least one expandable electrode is attached to said ridge.

17. A clip electrode for attachment to a nerve, comprising a pair of electrically non-conducting members secured together in a pivotal relation so as to form confronting jaws, wherein at least one electrode is attached to an electrically non-conducting member, and having a means for connection to an electric pulse means and wherein the electrode is shaped to avoid causing crush trauma to the nerve.

18. The clip electrode of Claim 17, wherein the electrode is concave so that the electrode contacts a nerve to avoid causing crush trauma.

19. The clip electrode of Claim 17, wherein the electrode is compressible so that the electrode contacts a nerve to avoid causing crush trauma.

20. The clip electrode of Claim 17, wherein the electrode is wire mesh or wire wool.

21. A cuff device for contacting an electrode with a nerve, comprising an electrode that conforms to a portion of a nerve to avoid causing crush trauma, and having a means for connection to an electric pulse.

22. The cuff device of Claim 21, further comprising at least one electrically non-conductive member having a traversing channel and the electrode located therein.

23. The cuff device of Claim 21, wherein the electrode is a wire mesh or wire wool.

24. An electrode array device for delivering a transdermal electric pulse to a nerve comprising electrically non-conductive material having a plurality of electrodes thereon, wherein the electrodes are electrically connected to a means of supplying an electric pulse.

25. The electrode array device, further comprising a conductive composition so that the electric pulse is transferred to the skin of a human or animal.

26. The electrode array device of Claim 24, wherein the electrically non-conductive material is sized and shaped for placement around a patient's neck and over the patient's vagus nerve.

27. The electrode device of Claim 26, wherein the device has laterally extending members for placement around a patient's neck.

28. An endotracheal tube electrode device comprising an endotracheal tube having an inflatable means of expanding an electrode, and at least one electrode thereon so that the electrode contacts the tracheal wall when the means of expanding the electrode is inflated, and wherein the electrode has a means for connection to an electrical pulsing means.

29. The endotracheal tube electrode of Claims 28, wherein the inflatable means of expanding an electrode is a collar or balloon.

30. The endotracheal tube electrode of Claim 29, wherein the balloon has a ridge and an electrode on said ridge so that the electrode contacts the tracheal wall when the collar is inflated.

31. The endotracheal tube electrode of Claim 28, further comprising a plurality of electrodes.

32. An endotracheal tube electrode device comprising an endotracheal tube having at least one expandable electrode thereon, so that the electrode contacts the tracheal wall when the electrode is expanded, and wherein the electrode has a means for connection to an electrical pulsing means.

33. The endotracheal tube electrode of Claim 32, further comprising a plurality of electrodes.

34. The endotracheal tube electrode of Claim 32, wherein the expandable electrode is longitudinally arranged.

35. The endotracheal tube electrode of Claim 32, wherein the expandable electrode is circumferentially arranged.

36. The endotracheal tube electrode of Claim 32, wherein the expandable electrode is spirally arranged.

37. The endotracheal tube electrode of Claim 32, having from 2-12 electrodes.

38. The endotracheal tube electrode of Claim 32, wherein the expandable electrode is an electrode selected from the group consisting of a wire, a basket, a strip, or a plurality of electrodes dispersed on an electrically non-conducting material.

39. The endotracheal tube electrode of Claim 32, wherein the expandable electrode comprises a proximal region, a central region and a distal region, and wherein when the electrode is expanded the proximal

region and the central region form a first angle between about 1° and 180°, and the central region and the distal region form a second angle of between about 1° and 180°.

40. The endotracheal tube electrode of Claim 32, wherein the first and second angles are between about 90° and 180°.

41. A nasogastric tube electrode comprising a nasogastric tube having an inflatable means of expanding an electrode and an electrode attached to said collar so that when the collar is inflated, the electrode contracts the inner surface of the esophagus, and a means of supplying an electric pulse to said electrode.

42. The nasogastric tube electrode of Claim 41, wherein the inflatable means of expanding the electrode is a collar or balloon.

43. The nasogastric tube electrode of Claim 41, wherein the balloon has a ridge and an electrode on said ridge so that the electrode contacts the tracheal wall when the collar is inflated.

44. The nasogastric tube electrode of Claim 41, further comprising a plurality of electrodes.

45. An nasogastric tube electrode device comprising an endotracheal tube having at least one expandable electrode thereon, so that the electrode contacts the tracheal wall when the electrode is expanded, and wherein the electrode has a means for connection to an electrical pulsing means.

46. The nasogastric tube electrode of Claim 45, further comprising a plurality of electrodes.

47. The nasogastric tube electrode of Claim 45, wherein the expandable electrode is longitudinally arranged.

48. The nasogastric tube electrode of Claim 45, wherein the expandable electrode is circumferentially arranged.

49. The nasogastric tube electrode of Claim 45, wherein the expandable electrode is spirally arranged.

50. The nasogastric tube electrode of Claim 45, having from 1-24 electrodes.

51. The nasogastric tube electrode of Claim 45, wherein the expandable electrode is an electrode selected from the group consisting of a wire, a basket, a strip, or a plurality of electrodes dispersed on an electrically non-conducting material.

52. The nasogastric tube electrode of Claim 45, wherein the expandable electrode comprises a proximal region, a central region and a distal region, and wherein when the electrode is expanded the proximal region and the central region form a first angle between about 1° and 180°, and the central region and the distal region form a second angle of between about 1° and 180°.

53. The nasogastric tube electrode of Claim 45, wherein the first and second angles are between about 90° and 180°.

54. An apparatus for the generation of controlled intermittent asystole comprising:

(a) an interrogator means;

(b) a cardiac pacer means electrically linked to said interrogator means;

(c) a cardiac monitoring means electrically linked to said interrogator means;

(d) a pulse generator means electrically linked to said interrogator means;

(e) a means of administering an effective dose of pharmaceutical composition to a patient to prolong cardiac asystole, wherein the means of administration is electrically linked to said interrogator means;

wherein the interrogator automatically sends a signal to the electrode and observed the response on the cardiac monitoring means to determine optimum location of the electrode.

55. The apparatus of Claim 54 further comprising a manually operable switch means electrically linked to the interrogator means to control either the pulse generator means or the cardiac pacer means.

56. The apparatus of Claim 54, wherein the cardiac monitoring means is selected from the group comprising an electrocardiograph, a blood pulse monitor, a blood pressure monitor and sphygmomanometer as a means of detecting and measuring cardiac vascular flow output.

57. The apparatus of Claim 54, wherein the interrogator receives an electric output signal from the cardiac monitoring means and determines an optimal output electric pulse.

58. The apparatus of Claim 54, wherein the manually operable switch means is a foot operated switch, a hand operated switch or a voice operated switch.

59. The apparatus of Claim 54, wherein the means of delivering an electric pulse from the pulse generator means to the patient is selected from an intravenous catheter, a clip electrode, a cuff electrode, an electrode array, an endotracheal tube electrode, and a nasogastric balloon electrode.

60. A method of inducing and prolonging asystole comprising the steps of::

(a) placing a catheter or tube having an expandable electrode into a blood vessel, trachea, or esophagus of a human or animal or placing a cutaneous electrode on the skin of the human or animal;

(b) positioning the electrode adjacent to the vagus nerve;

(c) administering to the human or animal a pharmaceutic composition comprising an acetylcholinesterase inhibitor, a β-adrenogenic receptor blocker and a calcium channel blocker;

(d) stimulating the vagus nerve with an electrical signal to the electrode;

(e) monitoring the cardiac output of the human or animal;

(f) stimulating the vagus nerve with another electrical signal to the electrode;

(g) monitoring the cardiac output of the human or animal; and

(h) determining the optimum electrode stimulation to induce and prolong asystole.

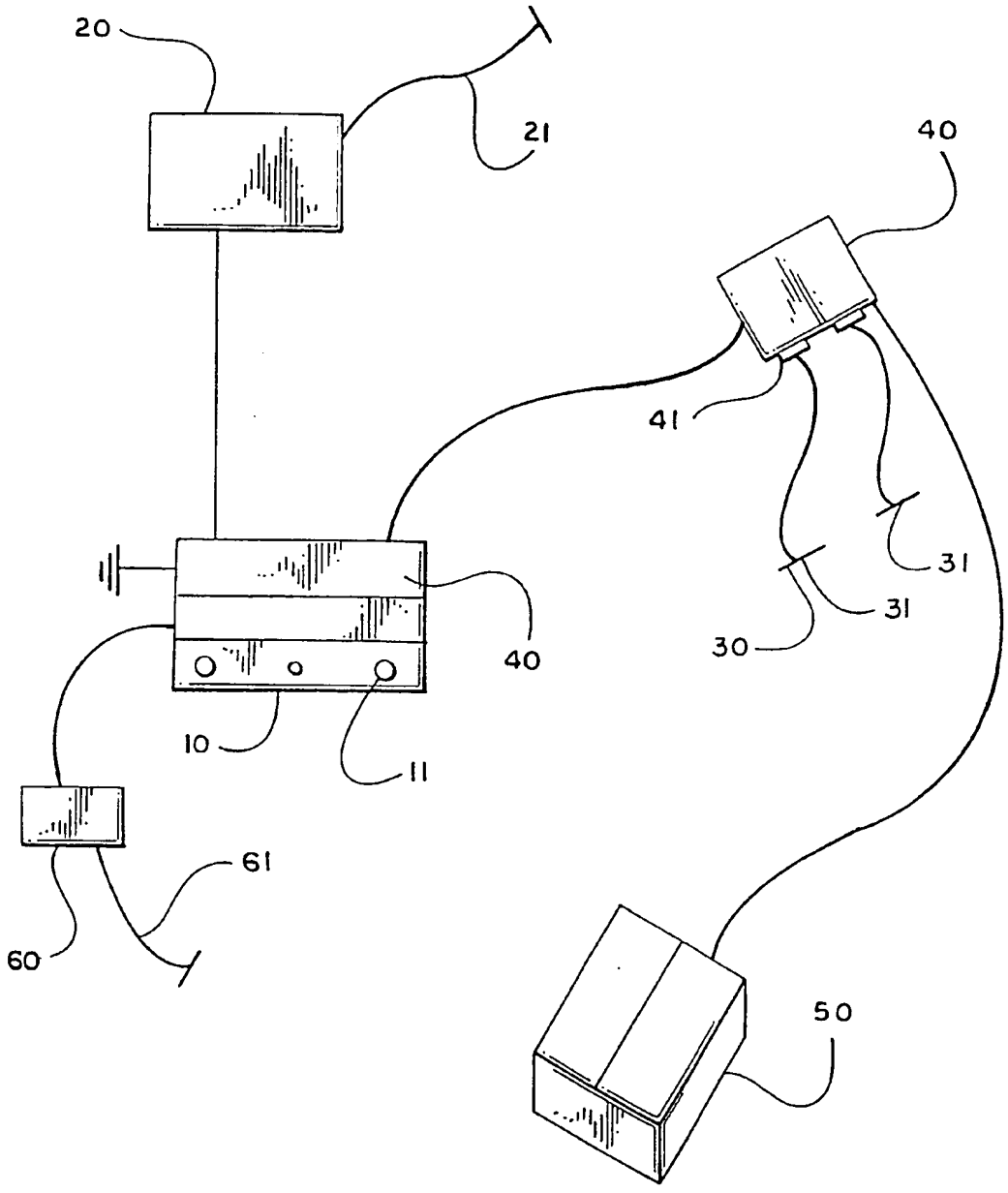


Fig_1

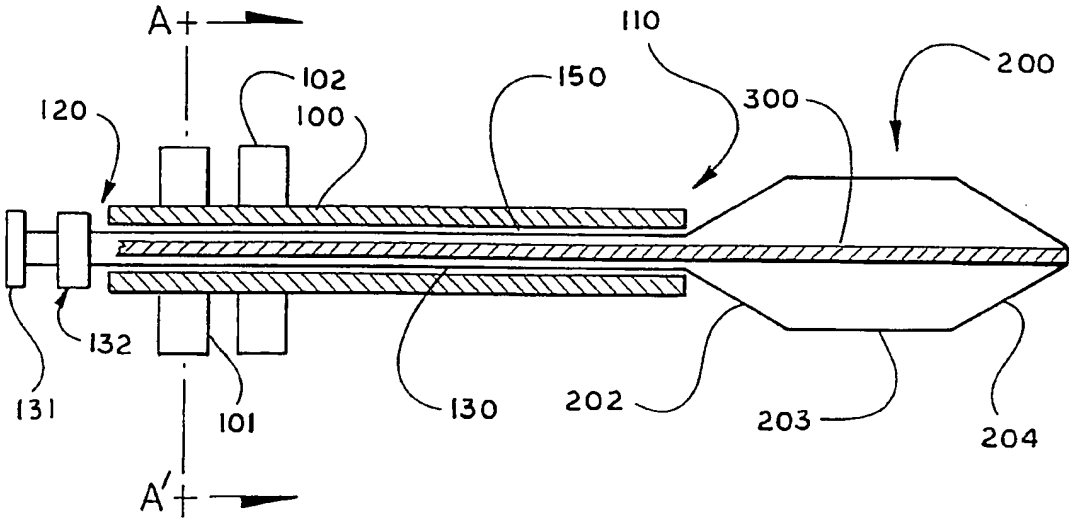

A+
110
200
102
150
120
100
300
132
131
101
130
202
203
204
A'+

Fig_2A

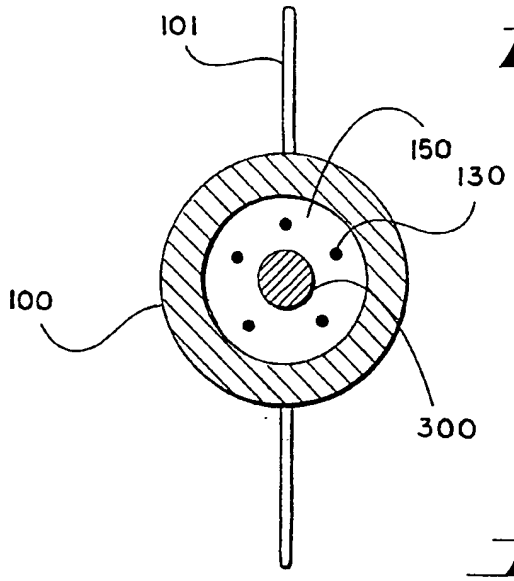
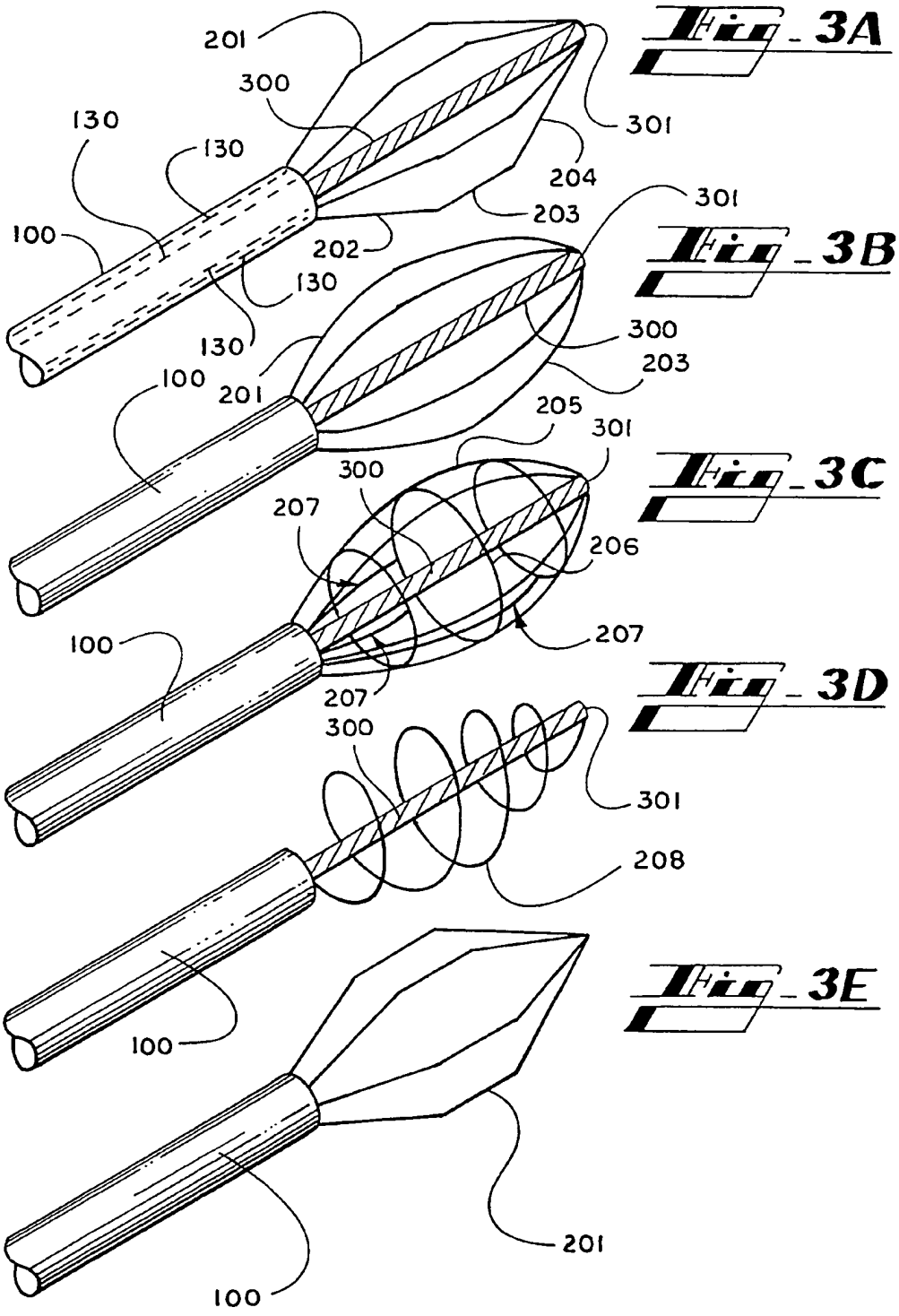

101
150
130
100
300

Fig_2B


201
300
130
130
301
204
203
100
202
130
130
Fig_3A
301
300
203
100
201
205
301
Fig_3B
300
207
206
207
100
207
Fig_3C
300
301
208
100
Fig_3D
201
100
Fig_3E

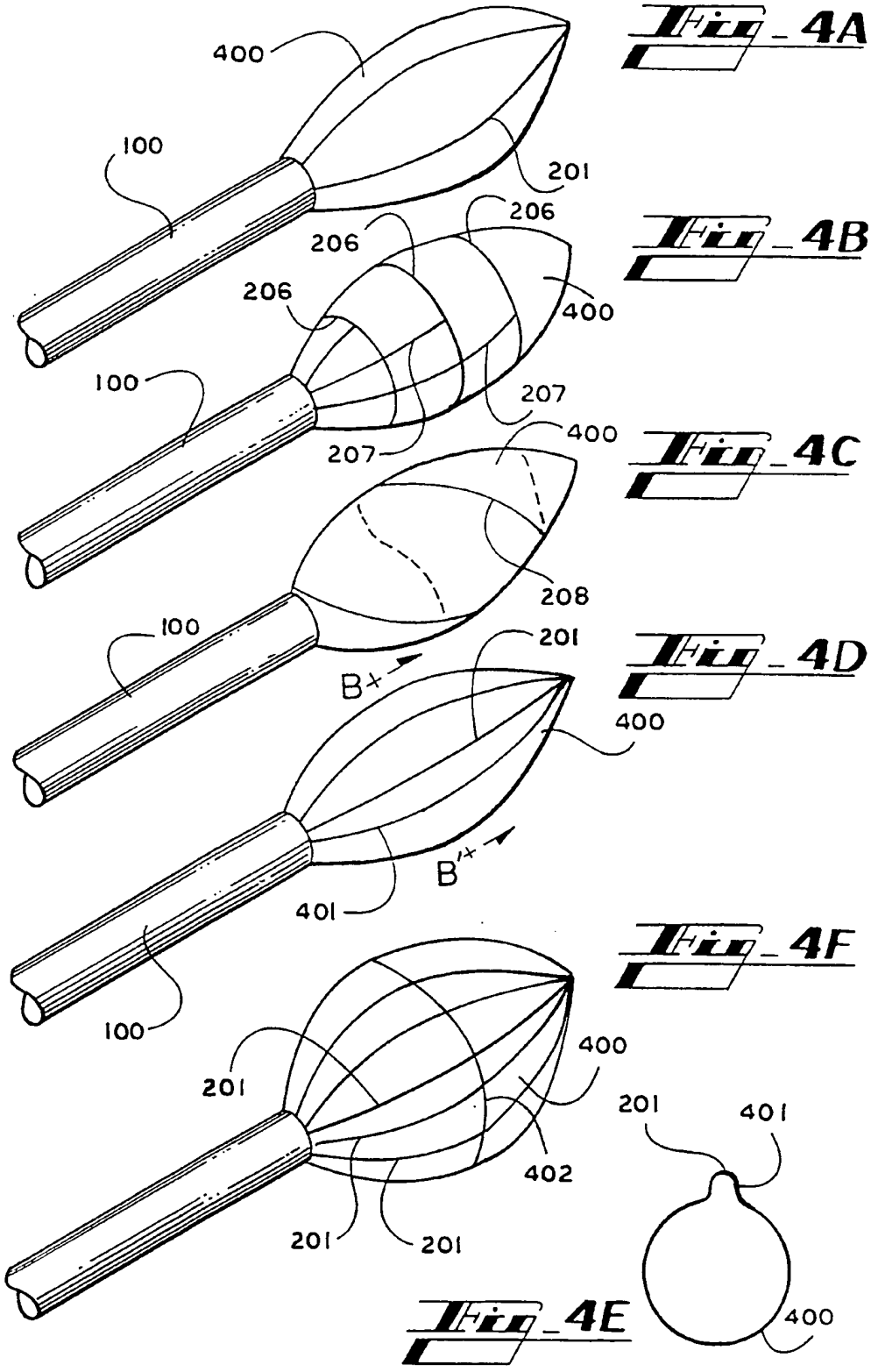


Fig_4A

Fig_4B

Fig_4C

Fig_4D

Fig_4F

Fig_4E

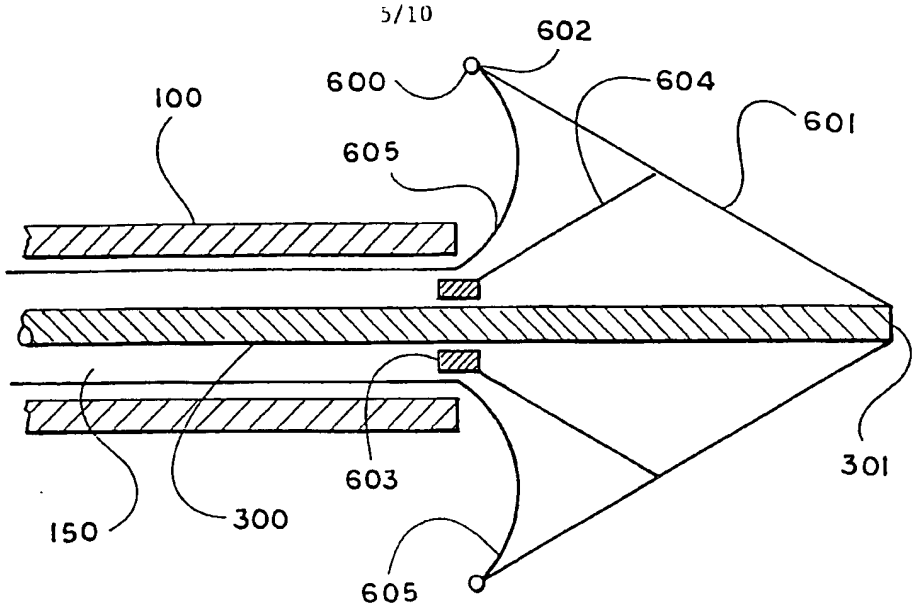
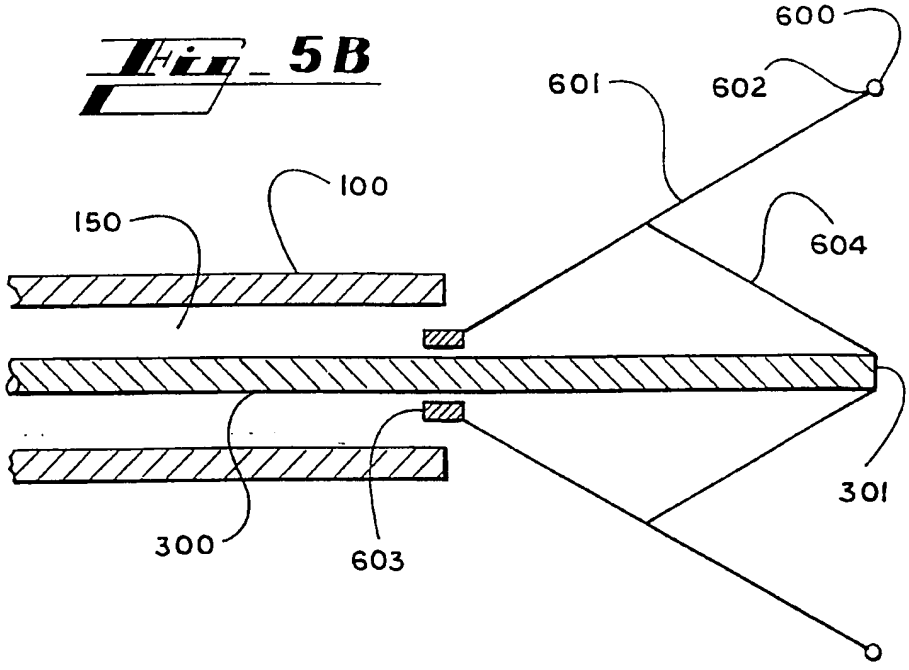

602
600
604
100
601
605
603
301
150
300
605

Fig_5A

Fig_5B


600
601
602
100
150
604
301
300
603

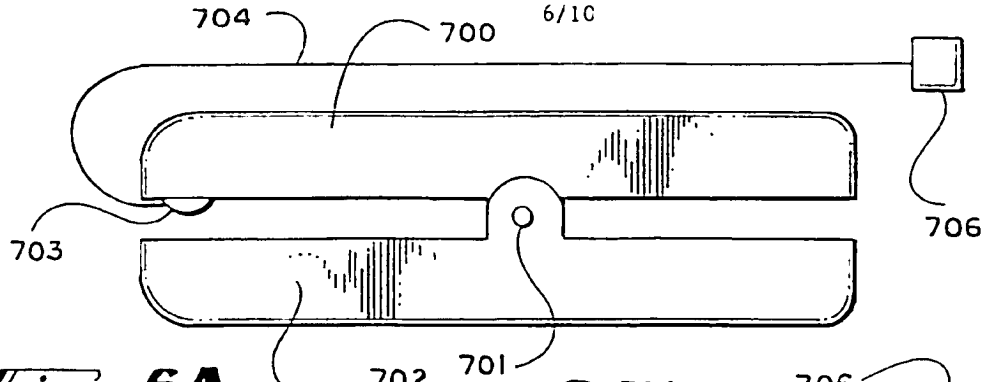


Fig_6A

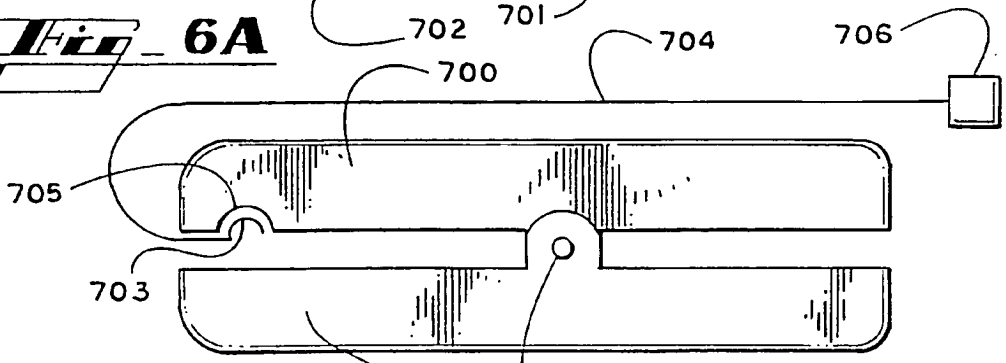


Fig_6B

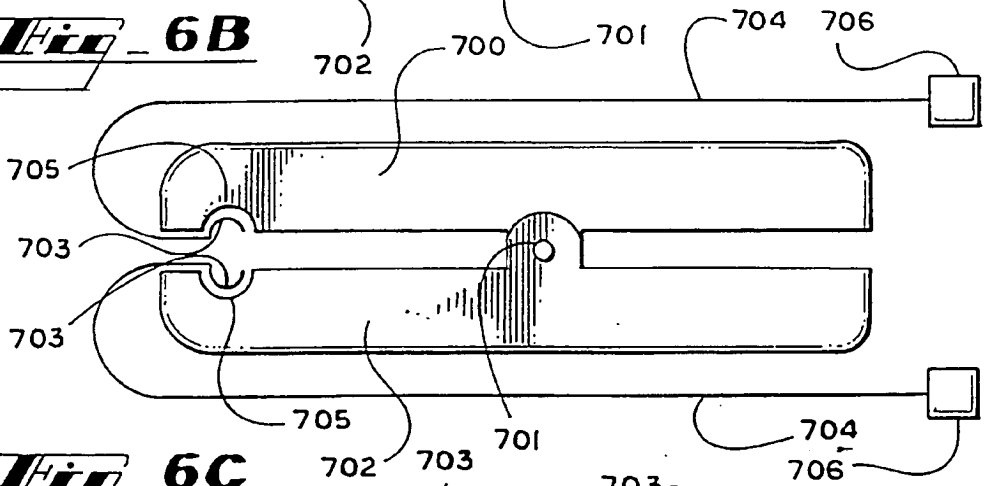


Fig_6C

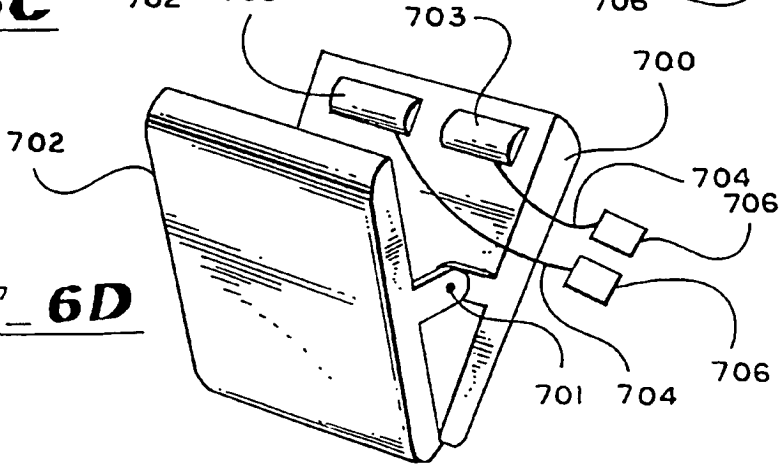


Fig_6D

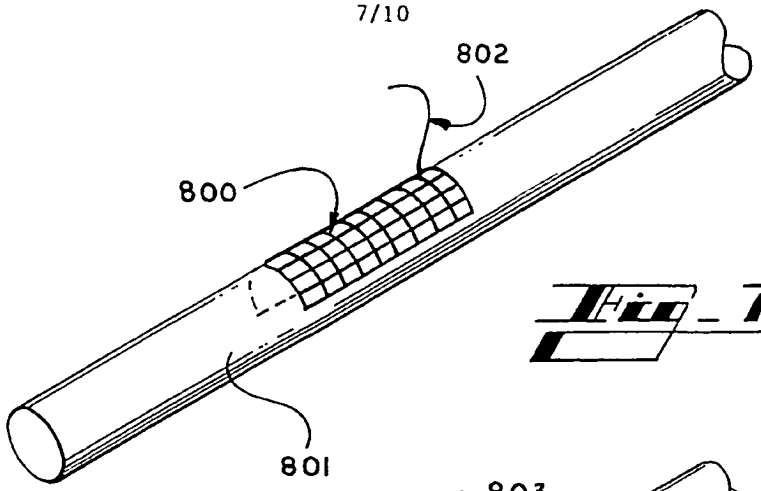


Fig_7A

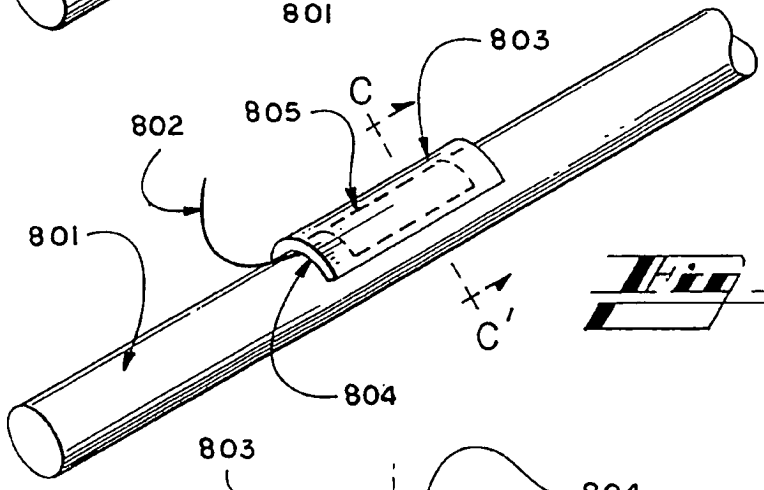


Fig_7B

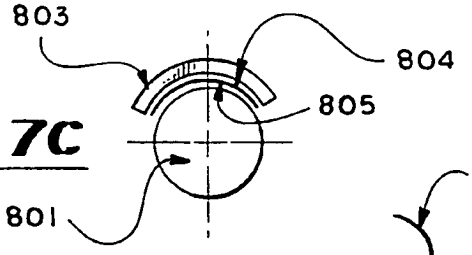


Fig_7C

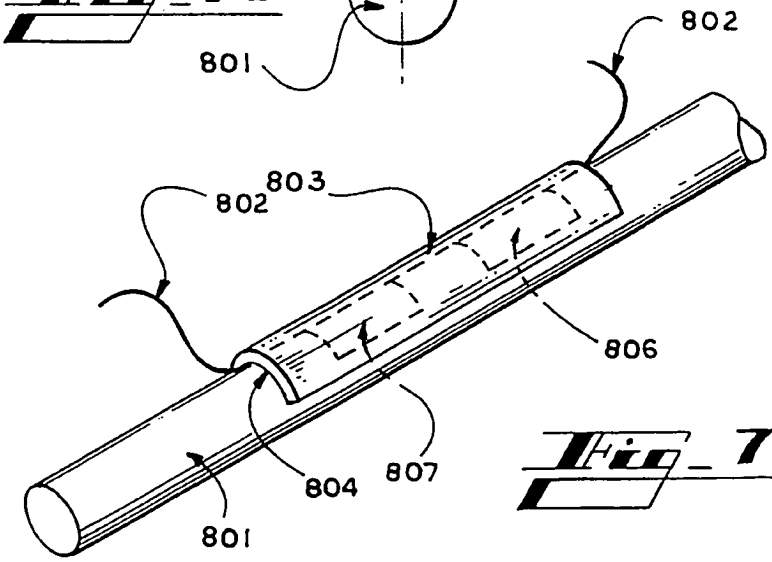


Fig_7D

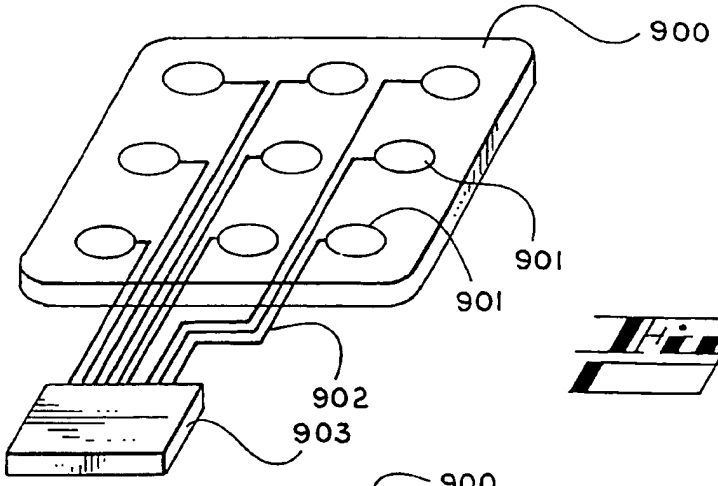


Fig_8A

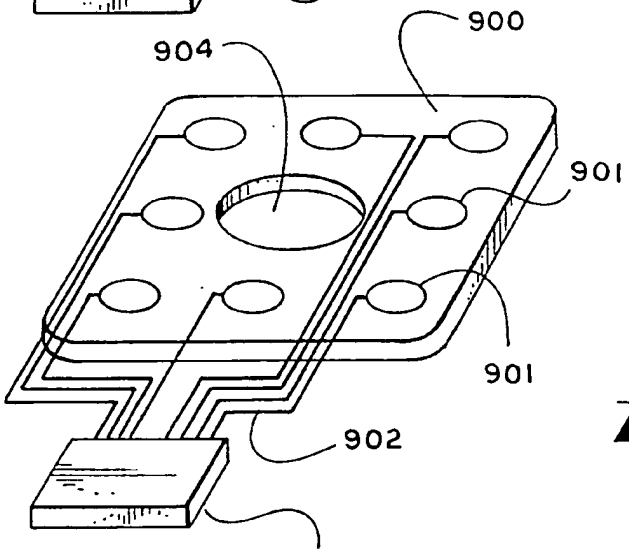


Fig_8B

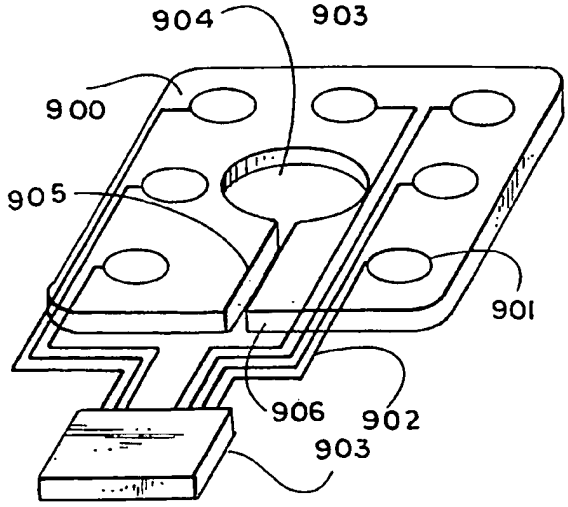


Fig_8C

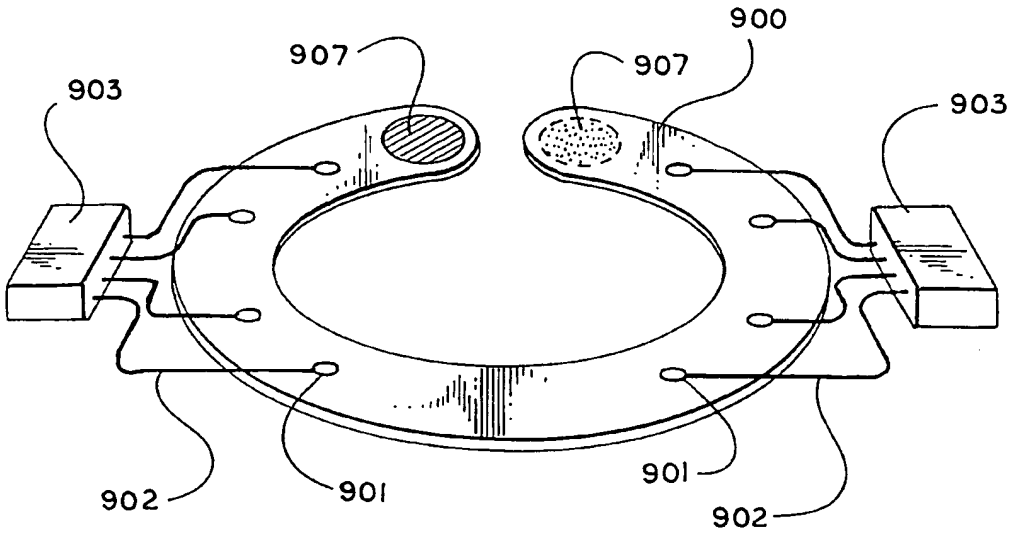


Fig_8D

Fig_8E

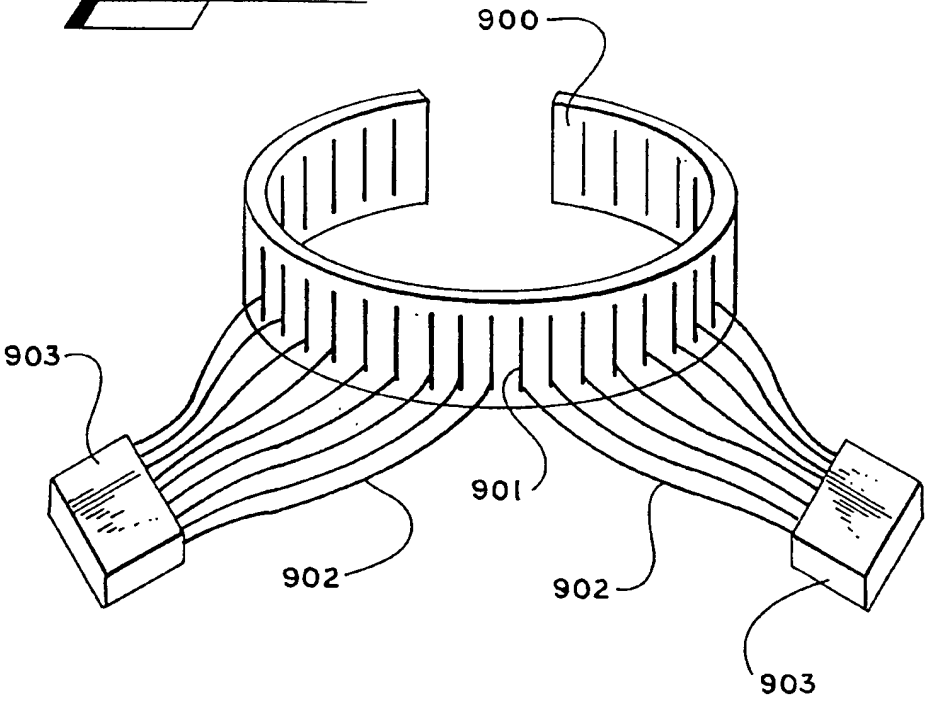
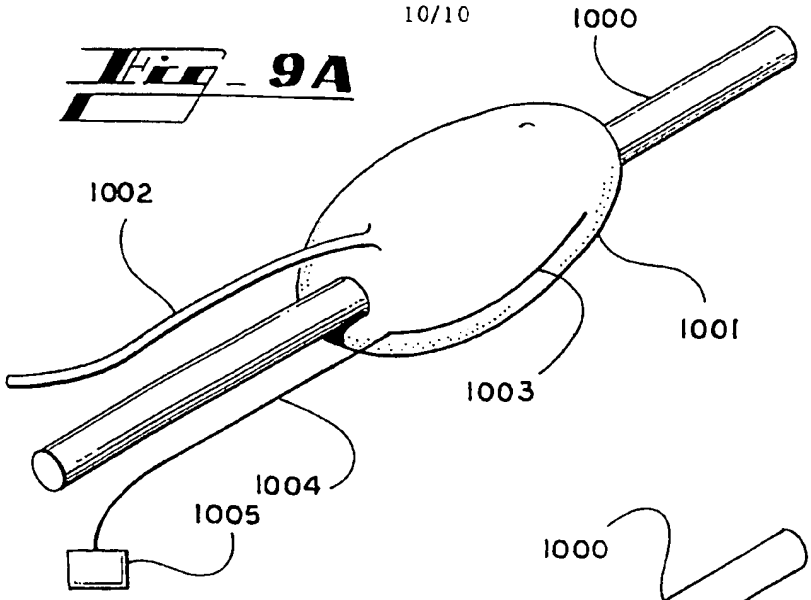


Fig_ 9A



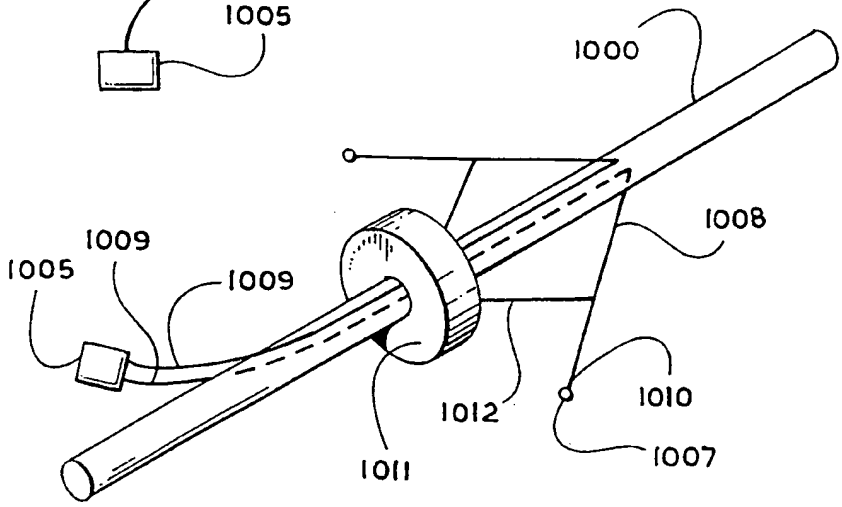


Fig_ 9B

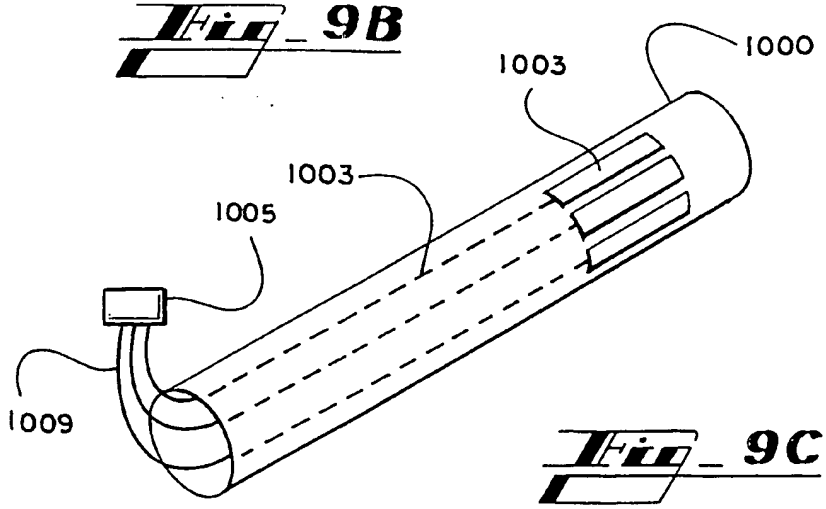


Fig_ 9C

INTERNATIONAL SEARCH REPORT

International application No
PCT/US00/17222

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61N 1/05
US CL :607/116
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 607/116-122

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,282,468 A (KLEPINSKI) 01 February 1994, entire document.	17-27
X	US 5,117,828 A (METZGER et al.) 02 June 1992, entire document.	1-16, 28-53
X	US 5,840,076 A (SWANSON et al.) 24 November 1998, entire document.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 SEPTEMBER 2000	12 OCT 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C 20231 Facsimile No. (703) 305-3230	Authorized officer GEORGE EVANISKO Telephone No. (703) 308-2612

Form PCT/ISA/210 (second sheet) (July 1998)*

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.